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British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 86 Number 5 May 2001

Editor-in-chief: Jennifer M. Hunter

- Risk factors for oesophagectomy
- Autologous blood transfusion during TKR
- Oxygen carriers

Journal of the Royal College of Anaesthetists

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start with it, ***stay*** with it, ***trust*** it

OxyContin® 10 mg, 20 mg, 40 mg, 80 mg tablets
PRESCRIBING INFORMATION
United Kingdom

Presentation
Film-coated, modified release tablets containing oxycodone hydrochloride, marked OC on one side and the stre th of oxycodone hydrochloride on the other. The 10 ng tablets are white and contain 10 mg of oxycodone hydrochloride (9 mg of oxycodone). The 20 mg tablets are pink, and contain 20 mg of oxycodone hydrochloride (18 mg of oxycodone). The 40 mg tablets are yellow, and contain 40 mg of oxycodone hydrochloride (36 mg of oxycodone). The 80 mg tablets are green, and contain 80 mg of oxycodone hydrochloride (72 mg of oxycodone). **Indications** For the treatment of moderate to severe pain in patients with cancer and post-operative pain. **Dosage and administration** OxyContin tablets must be swallowed whole, and not chewed. **Elderly and adults over 18 years:** OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements. The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. If higher doses are necessary, increases should be made, where possible in 25% - 50% increments. Patients transferring from morphine should have the daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine. For most patients the maximum dose of OxyContin tablets is 200 mg, 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000mg have been reported. **Children under 18 years:** Not recommended. **Contra-indications** Respiratory depression, head injur aralytic ileus, acute abdomen, delayed gastric empt g, chronic obstructive airways disease, chronic bron l asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment, chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy. **Precautions and warnings** A reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid dependent patients and in patients with raised intracranial pressure, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, chronic renal and hepatic disease, and debilitated patients. OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OxyContin tablets should be discontinued immediately. Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyContin tablets for 24 hours before surgery. If further treatment with OxyContin tablets is then indicated the dosage should be adjusted to the new post-operative requirement. OxyContin tablets should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. **Pregnancy and lactation** Not recommended. Oxycodone is secreted in breast milk and may cause respiratory depression in the newborn. OxyContin tablets should, therefore, not be used in breast-feeding mothers. **Side-effects** Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur. The most common adverse drug reactions seen during therapy are constipation (which may be prevented with an appropriate laxative), nausea, dizziness, pruritus, urticaria, vomiting, headac ry mouth, sweating, drowsiness and asthenia. If nausea and vomiting are troublesome oxycodone may be combined with an antiemetic. Occasional adverse reactions are anorexia, nervousness, insomnia, fever, confusion, diarrhoea, abdominal pain, vasodilation, dyspepsia, paraesthesia, rash, anxiety, euphoria, depression, dyspnoea, postural hypotension, chills, abnormal dreams, thought abnormalities, hiccups. Vertigo, twitching, gastritis, disorientation, facial flushing, mood changes, palpitations, hallucinations, bronchospasm and colic may occur in a few patients. Micturition may be difficult and there may be biliary or ureteric spasm. Overdose may produce respiratory depression. Rarely, clinically relevant reductions in blood pressure and heart rate have been observed. **Legal category** CD (Sch2) POM **Package quantities and price Blister packs of 56 tablets** 10 mg - £21.43 20 mg - £42.86 40 mg - £85.73 80 mg - £171.46. **Marketing Authorisation numbers** PL 16950/0097-0100.

Marketing Authorisation holder Napp Pharmaceuticals Limited Cambridge Science Park, Milton Road, Cambridge CB4 0GW UK Tel: 01223 424444 Member of the Napp Pharmaceutical Group Further information is available from Napp Pharmaceuticals Limited.

Date of preparation: December 2000

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Louisville, KY 40202, USA
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Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

European Academy of Anaesthesiology Award Programme

1. EAA Clinical Scholar Research Award

This award is created to further the understanding of anaesthesiology and related sciences of clinical practice through clinical investigations. Research must involve human subjects. The maximum amount to be awarded for any project is 25 000 Euro. Please note that institutional indirect expenses are not funded.

To qualify, the principal applicant must be a member of the European Academy of Anaesthesiology (EAA) and be an investigator with a research record who has yet to establish a history of substantial funding. The award will go to a research project, which is judged by peer review to have high scientific merit and high probability of success. Priority funding will be awarded to proposals which are independent of other grant support. Experienced investigators working in new areas will receive consideration. The proposed project must have direct relevance to the speciality of anaesthesiology. Applicants must submit their curriculum vitae as well as an outline of their proposed research project. Furthermore, the application should be accompanied by a letter from the chairman of the department outlining the applicant's research qualities.

2. EAA Teaching Recognition Award

The purpose of this award is to discover an individual with outstanding teaching skills besides his/her research skills. The award winner will be required to give a total of five lectures. One lecture must be presented at the annual EAA congress. The other four lectures will be given in each of four different European countries, either at university departments or at the annual congress of the national societies. The award winner will receive a travel reimbursement for every lecture up to 1250 Euro. The remaining travel expenses will be paid by the host departments or congress organizers, if necessary. The maximum amount to be awarded is 5000 Euro.

Applicants should not be older than 45 years and should have finished their PhD or an equivalent degree. To qualify, applicants must be a member of the EAA. Applicants must submit their curriculum vitae as well as an outline of their lecture. Each application must be accompanied by a letter from the applicant's chairman, and two letters from residents in their own department, outlining the applicant's teaching qualities.

3. EAA Training Award

This award is created for young anaesthetists, including residents in their last year of training, with the aim of completing their training in another European department of anaesthesiology, recognized as a European centre for training of anaesthesiologists. The winner of the award will receive 2000 Euro per month for a maximum of six months.

To qualify, the applicant must have passed at least the Part I of the European Diploma of Anaesthesiology or be a member of the EAA. Candidates must submit a curriculum vitae as well as a description of the special training which they intend to follow. Furthermore, each application must be accompanied by a letter from his/her chairman as well as a letter from the chairman of the host department.

Please submit one original application and six copies to the EAA Secretary, **before April 30, 2001.** Prof. Dr. Th. Pasch, Universitats Spital Zürich, Direktor des Institut für Anästhesiologie, Rämistraße 100, CH-8091 Zürich, Switzerland.

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, March 23, May 4, July 6, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

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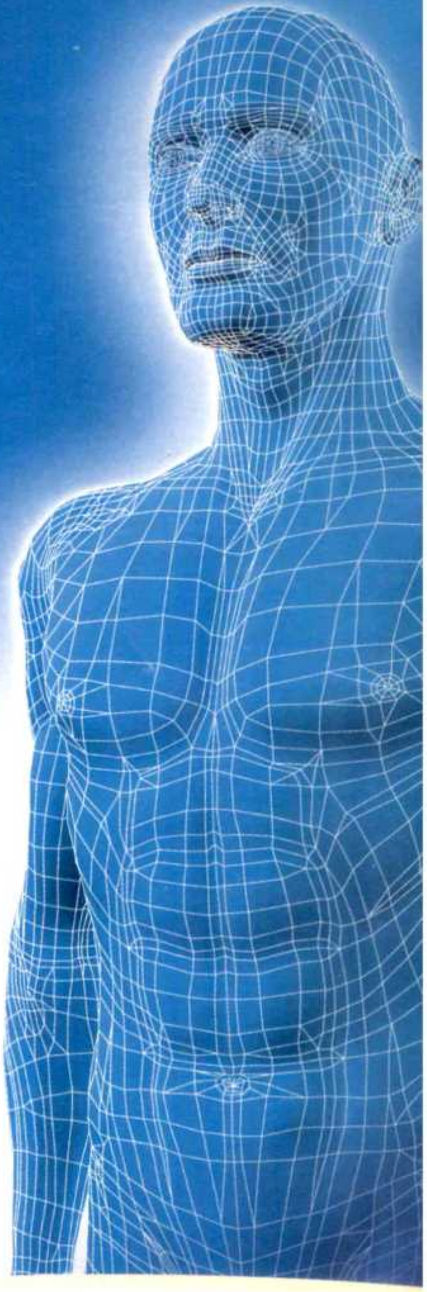

Final FRCA Revision Course

Leicester Royal Infirmary, Leicester, UK, May 1–4, 2001

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice. Course director: Dr Paul Sharpe.

Fees: £290 Non-residential (including lunch and refreshments); £390 Residential at local hotel (including lunch and refreshments).

For a booking form please contact Christine Gethins, Tel: 0116 258 5291 (places strictly limited).

Combined Scientific Meeting (CSM 2001) of The Australian and New Zealand College of Anaesthetists (Faculty of Intensive Care and Faculty of Pain Medicine) and The Hong Kong College of Anaesthesiologists

Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

Developments and Controversies in Intensive Care—a one day symposium

Maritime Museum, Liverpool, UK, May 11, 2001

Organized by the University Department of Anaesthesia in conjunction with the Mersey School of Anaesthesia and the Association of Merseyside Intensive Care Units.

For further information, please contact: Joyce Coleman, Tel: 0151 293 2202 or Sue Costigan, Tel: 0151 293 2396

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail:akabogu@mcn-nuernberg.de; www: http://www.mcn-nuernberg.de

Annual Symposium Dental Sedation Teachers Group

Sedation in the 21st Century

The Village Hotel and Leisure Club, Cardiff, UK, Tuesday May 22, 2001

The group provides a forum for all individuals who are interested in the teaching of conscious sedation in dentistry. The membership includes dental and medical practitioners from university, hospital, community and general practice backgrounds. The programme is designed to allow an interchange of views on the use of conscious sedation in dentistry. For further details please visit our website: www.dstg.co.uk

Speakers: Dr P. Averley, Dr G. Lahud, PDS Initiative Billingham; Dr C. Bell, Dept of Oral Surgery, Bristol Dental School; Dr I. Cooper, Department of Health; Dr D. Craig, Associate Specialist, GKT; Dr A. Neilson, Associate Specialist, Dundee Dental School; Dr D. Vaughan, Senior Dental Officer, MPhil student, Cardiff; Dr M. Wilson, Senior Lecturer in Restorative Dentistry, Manchester; C. Pennell, E. Williams, A. Millard-Davis, Cardiff Sedation Nurses.

Organiser: Dr N. D. Robb, Sedation Suite, UWCM Dental School, Heath Park, Cardiff CF14 4XY, UK. E-mail: robbnd-@cardiff.ac.uk

Symposium Venue: Village Hotel and Leisure Centre, 29 Pendwyallt Road, Coryton, Cardiff CF14 7EF, UK. Tel: 02920524300; Fax: 02920524313; E-mail: village.car@cybase.co.uk; Website: www.vhl.co.uk

Accommodation: Contact hotel and mention DSTG. Rate £75 B&B including use of leisure facilities.

Registration: Members £55 Non-members £65. Annual symposia are open to members and non-members. Attending non-members will be offered one year's membership of the group included in the registration fee.

Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, UK, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
Tel: 01442 879000. Fax: 01442 870999.

E-mail: enquiries@prestige-promotions.co.uk

5th International Conference on Memory, Awareness and Consciousness: Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, NY, June 1–3, 2001

For further information, please contact: (for scientific enquiries) Ruth Reinsel, PhD, Department of Anesthesiology and Critical Care, Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6038; Fax: +1 212 772 8646; E-mail: mac@mskcc.org; website: www.maacc.org or (for other enquiries) Office of Continuing Medical Education, Box 31, Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6754; Fax: +1 212 717 3140; E-mail: cmeinfo@mskcc.org; website: www. mskcc.org

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92; E-mail: SSAI.2001@rito.no
Web site: www.ssai2001.org

7th International Neuromuscular Meeting

Belfast, UK, June 21–24, 2001

For further information, please view the website http://www.nisca.org/nmb2001/ or contact Professor R. K. Mirakhur, Department of Anaesthetics and Intensive Care Medicine, The Queen's University of Belfast, Whitla medical Building, 97 Lisburn Road, Belfast BT9 7BL, Tel: 44 (0) 28 9033 5785; Fax: 44 (0) 28 9032 9605; E-mail: r.mirakbur@qub.ac.uk.

Abstracts are invited for presentation at the meeting. Please visit the website for instructions.

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Ventilation Through the Ages

ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

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To be placed on the list for registration details, please contact: Sue Hubbard, ERMEC, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK. Tel +44 (0)1482 674007; Fax: +44 (0)1482 586587; E-mail: suehermec@hotmail.com

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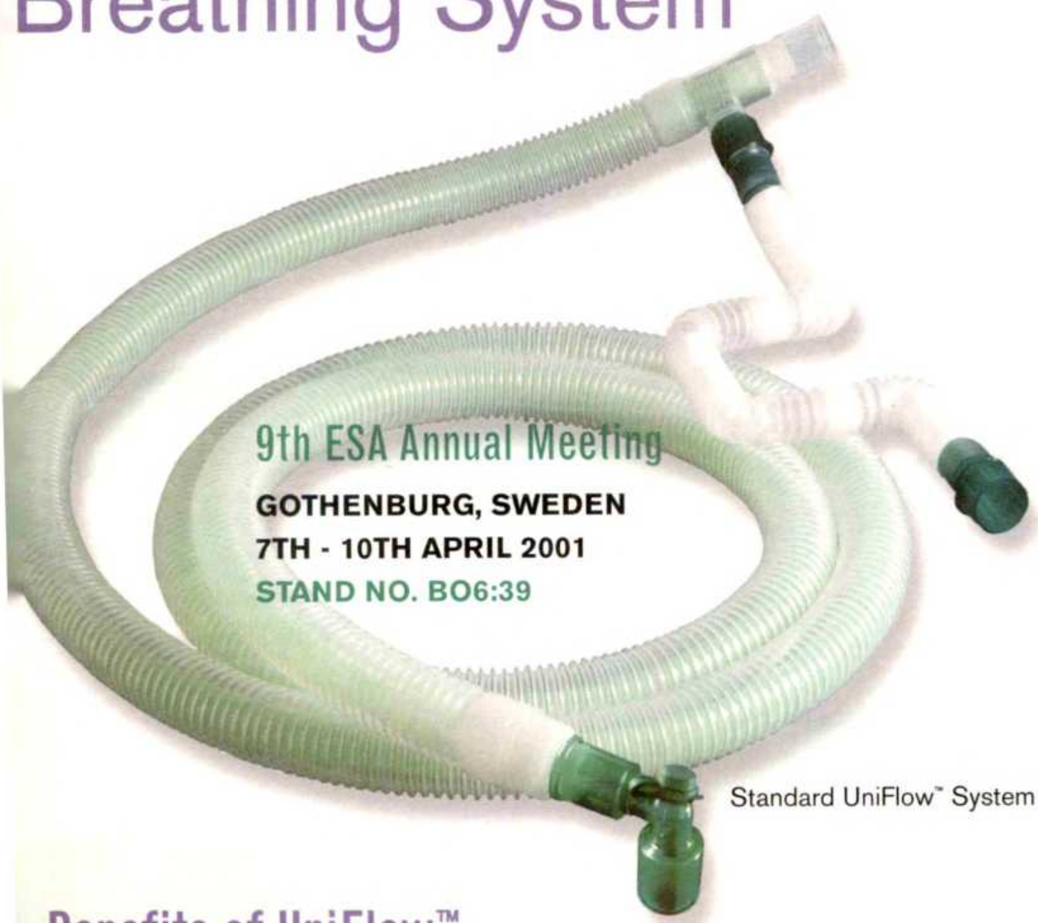

9th ESA Annual Meeting
GOTHENBURG, SWEDEN
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Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 2604472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

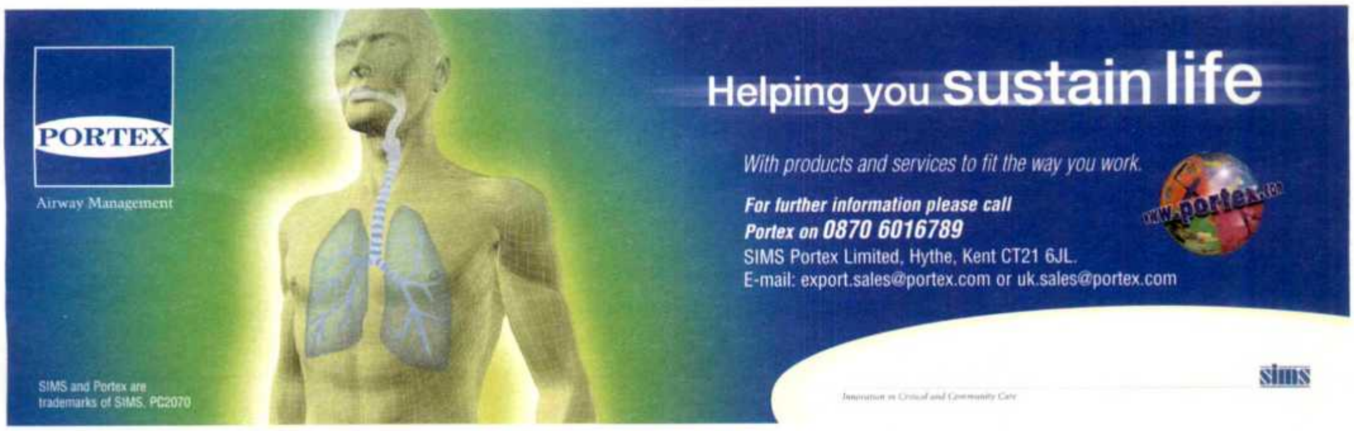
Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003



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IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia

19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib. VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded. *Elderly:* Exercise care when increasing the dose from 12.5 mg to 25 mg. *Hepatic insufficiency:* In mild hepatic insufficiency, do not exceed 12.5 mg once-daily. *Children:* Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs.

Third trimester of pregnancy and lactation. Inflammatory bowel dise
Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existi
significantly impaired renal function, uncompensated heart failu
or cirrhosis. Use caution when initiating treatment in patients w
considerable dehydration. Rehydrate patients prior to starti
therapy with rofecoxib. Consider the possibility of fluid retention a
exercise caution when rofecoxib is used in patients with pre-existi
oedema, a history of heart failure, left ventricular dysfunction
hypertension. Maintain appropriate supervision when treating t
elderly or patients with renal, hepatic or cardiac dysfunction wi
rofecoxib. In clinical studies, some osteoarthritis (OA) patients treat
with rofecoxib developed perforations, ulcers or bleeds (PUB
Patients with a prior history of a PUB and patients greater than
years of age appeared to be at a higher risk for a PUB. At d[illegible] dos
higher than 25 mg, the risks of gastro-intestinal symptoms, oeden
or hypertension are increased. Elevations of ALT and/or AST ≥
times the upper limit of normal) have been reported in approximate
1% of patients in clinical trials with rofecoxib. Any patient wi
symptoms and/or signs suggesting liver dysfunction, or in whom a
abnormal liver function test has occurred, should be evaluated f
persistently abnormal liver function tests. If persistently abnormal liv
function tests (three times the upper limit of normal) are detecte
discontinue rofecoxib. Rofecoxib may mask fever. Use of rofecoxi

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Landmark study supports superior GI safety profile compared with conventional NSAIDs

50% reduction in perforations, ulcers and bleeds (PUBs) compared with naproxen (95% CI 0.3-0.6; p=0.001)

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Rarely, patients may develop perforations, ulcers and bleeds with VIOXX, but the risk is lower in patients treated with VIOXX than in patients treated with conventional NSAIDs.

'VIOXX' IS LICENSED FOR OSTEOARTHRITIS ONLY, AT A DOSE OF 12.5 mg OR 25 mg ONCE DAILY

harmacodynamic): Warfarin: closely monitor the prothrombin time NR when therapy with rofecoxib is initiated or changed in patients eceiving warfarin or similar agents, particularly in the first few days. *CE-inhibitors:* administration of 25 mg daily of rofecoxib with enazepril, 10 mg to 40 mg daily for four weeks to patients with ypertension was associated with a small attenuation of the ntihypertensive effect compared to the ACE inhibitor alone. This hould be considered in patients taking rofecoxib concomitantly with CE inhibitors. *Beta-blockers and diuretics:* concomitant use of SAIDS may reduce the antihypertensive efficacy of beta-blockers nd diuretics and the other effects of diuretics. *Aspirin:* at steady state, ofecoxib 50 mg once-daily had no effect on the anti-platelet activity f low-dose (81 mg once-daily) aspirin. Avoid concomitant dministration of rofecoxib with higher doses of aspirin or other SAIDS. *Cyclosporin/tacrolimus:* monitor renal function when ofecoxib and either cyclosporin or tacrolimus is used in combination. *nteractions (pharmacokinetic): Lithium:* NSAIDS may increase lasma lithium concentrations. *Methotrexate:* consider adequate onitoring for methotrexate-related toxicity when rofecoxib and ethotrexate are administered concomitantly. *CYP1A2 substrates:* xercise care with concomitant administration of rofecoxib with drugs rimarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, crine and zileuton). *Midazolam:* a modest 30% reduction of the AUC f midazolam was seen with rofecoxib 25 mg daily, most likely due o increased first pass metabolism through induction of intestinal YP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a odest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25-mg dose when rofecoxib is used with potent inducers of hepatic metabolism. Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *Pregnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus. *Lactation:* contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity includin hepatic failure and jaundice.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspensi 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers:
Tablet 12.5 mg: PL 0025/0383. Tablet 25 mg: PL 0025/038 Oral Suspension 12.5 mg/5 ml: PL 0025/0385; Oral Suspensi 25 mg/5 ml: PL 0025/0386.

Marketing Authorisation holder: Merck Sharp & Dohme Limit Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** February 2001

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References:

1. Bombardier C, Laine L, Reicin A et al. Comparison of upp gastro-intestinal toxicity of rofecoxib and naproxen in patients w rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528.

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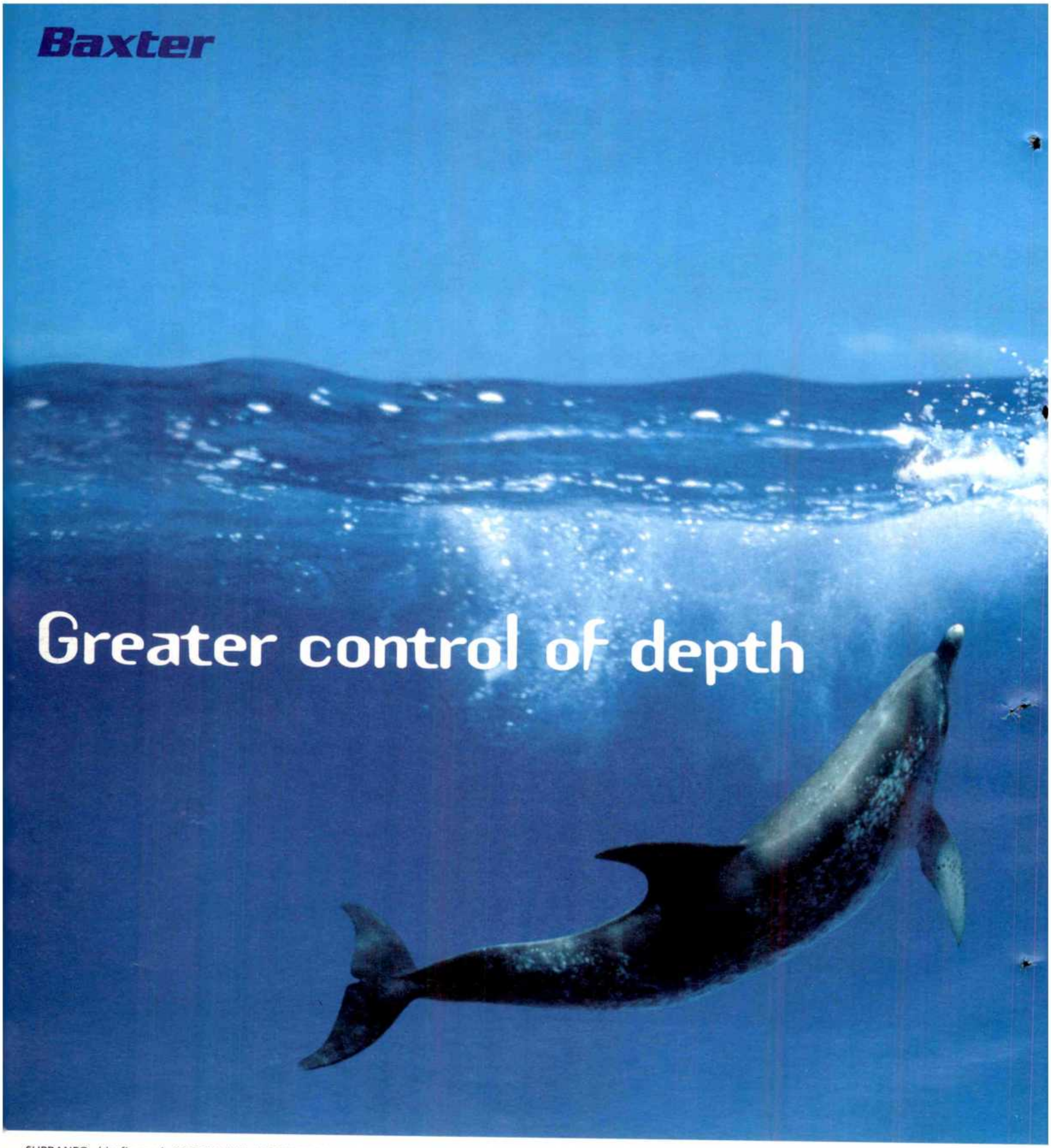
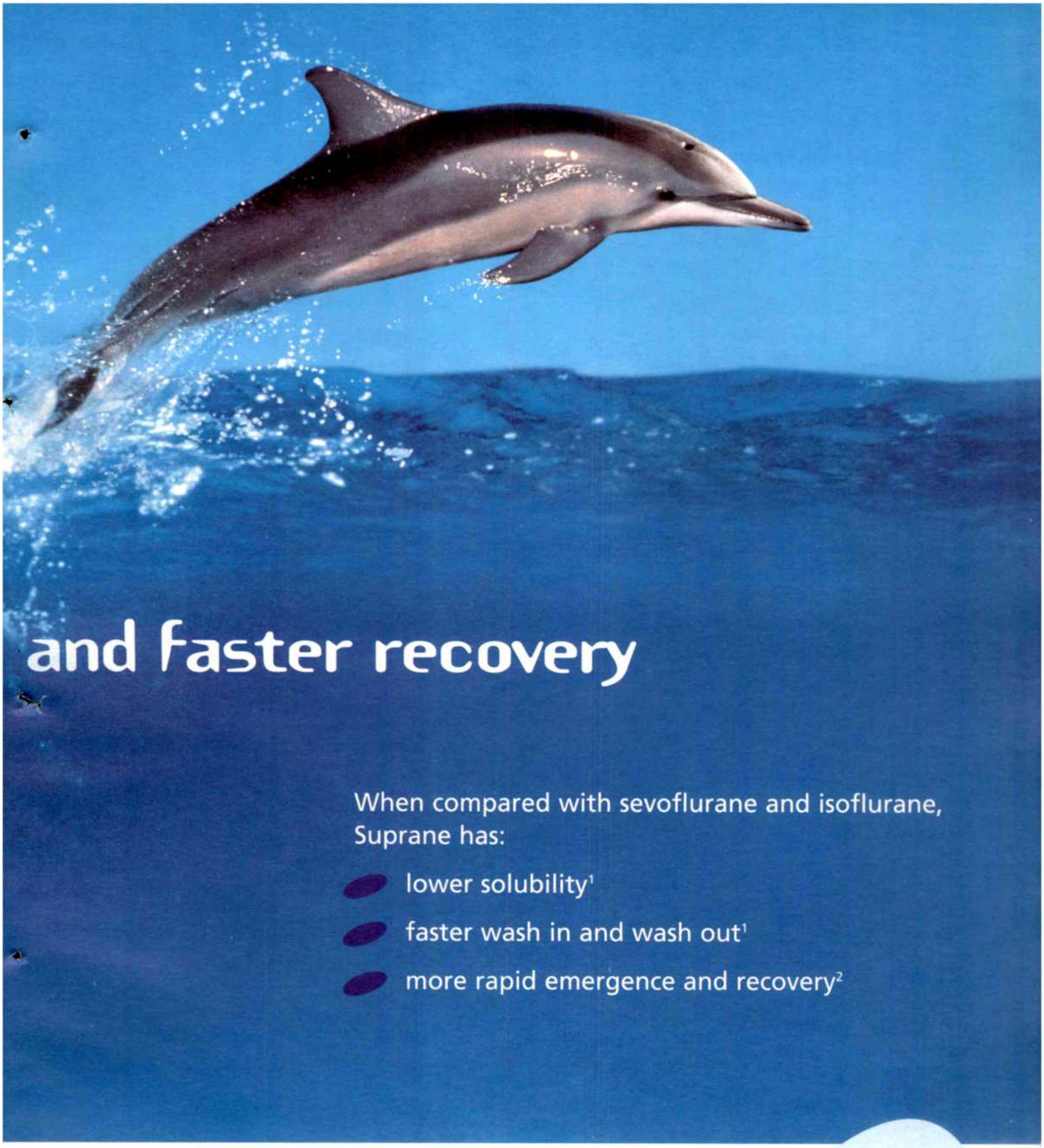


SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast


and faster recovery
When compared with sevoflurane and isoflurane, Suprane has:
lower solubility[1]
faster wash in and wash out[1]
more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

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SUP021/UK/0200

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Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss)

Dosage and administration:
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1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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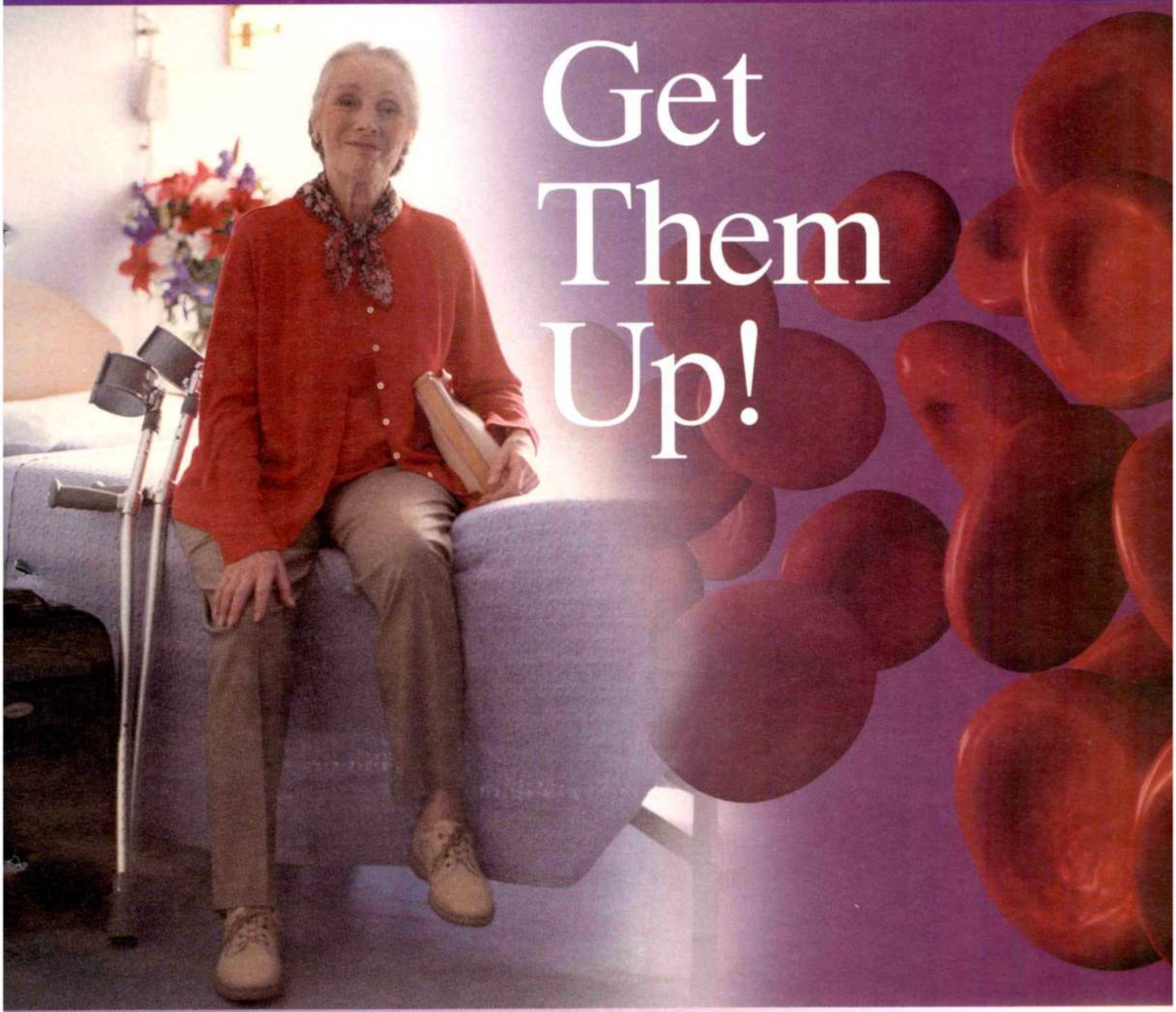

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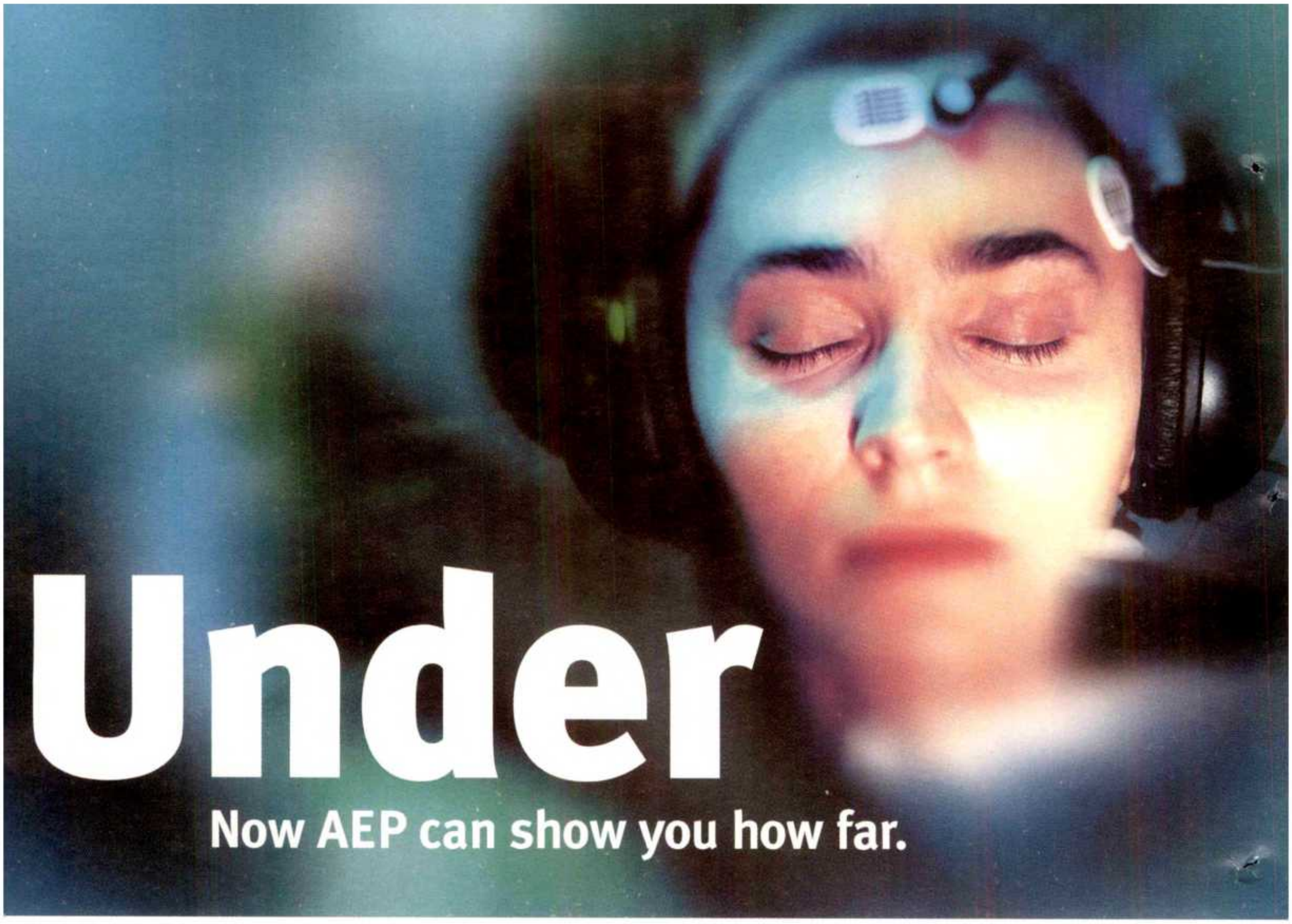
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BRITISH JOURNAL OF ANAESTHESIA

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Editorial I

Mapping the anatomy of unconsciousness—imaging anaesthetic action in the brain

The issue of how and where general anaesthetics act in the brain continues to intrigue and occupy researchers. Studies that address these issues can be focused at different levels. One reductionist approach is to investigate anaesthetic interactions with specific receptors or other molecular targets in a variety of models.[1–6] While such studies are important, they are difficult to interpret in the context of functional neuroanatomical models of consciousness.[7 8] An alternative approach is to consider the differential effects of anaesthesia on different brain areas, with a view to identifying specific brain regions that are important for anaesthesia (and by inference, for the generation of consciousness).

Such an assessment of spatial variations in general anaesthetic effects in the brain is not easy. While clinical measurement of anaesthetic effect has substantially depended on measuring spontaneous or evoked electrical responses,[7] current implementations cannot provide the tomographic visualization of subcortical physiology required to understand sites of anaesthetic action.[8 9] Magnetoencephalography (MEG) can provide detailed information regarding foci of brain activation,[10] but while the technique has been applied to pre-surgical planning,[11] there are no reports of MEG studies of anaesthetic action.

This inability to map primary brain function (i.e. electrical activity) has led researchers to image secondary physiological phenomena associated with neuronal excitation. As neuronal activity is closely coupled to glucose metabolism (and in many circumstances to blood flow), imaging the effect of anaesthetic agents on cerebral blood flow (CBF) and cerebral metabolic rates for glucose (CMRgluc) may provide surrogate measures of regional effects. Indeed, these indices have been investigated in several experimental studies of anaesthetic action in animal models using autoradiography with [^{14}C]iodoantipyrine and [^{14}C]deoxyglucose, respectively.[12–17] More recent experimental studies have used the newer technique of functional magnetic resonance imaging (fMRI) to map changes in regional CBF associated with anaesthetic effects.[18] Similar studies are now possible in humans with techniques such as positron emission tomography (PET) and fMRI.

The most common implementation of fMRI in this context uses blood oxygen level dependent (BOLD) contrast,[19 20] which depends on coupled increases in regional CBF associated with neuronal activation. It is now known that such CBF recruitment is associated with a *reduction* in proportional oxygen extraction, and a relative *increase* in regional oxygen saturation. The use of appropriate image acquisition protocols or 'sequences' translates these changes in regional oxygen saturation into areas of high signal intensity on subtraction images. These changes can be submitted to statistical analysis to identify areas of significant blood flow change, and inferences drawn about neural activation. The microcirculatory changes responsible for such fMRI contrast are crucially dependent on the maintenance of normal flow-metabolism coupling. While flow-metabolism coupling is retained to a substantial extent with many anaesthetics,[21] the relative difficulty of providing anaesthesia in MR environments has limited the application of fMRI to studies of anaesthetic action in humans. However, one recent fMRI study in human volunteers suggested that isoflurane impairs thalamo-cortical transmission of sensory information,[22] in keeping with previous electrophysiological studies in animal models.[8]

Positron emission tomography studies the distribution and kinetics of molecules that incorporate positron-emitting isotopes[23–25] such as $H_2{}^{15}O$, which is used to study blood flow, and ^{18}fluoro-deoxyglucose (^{18}FDG), which provides images of cerebral glucose uptake. Such studies provide maps of cerebral physiology and metabolism with sub-centimetre spatial resolution and a sufficiently small radiation burden (typically less than 5 mSv in the context of an annual background radiation in East Anglia of about 2 mSv) that allows application of the technique to healthy volunteers. While concomitant sampling of radioactivity in arterial blood can provide quantitative results, it is far more common in volunteer studies to acquire non-quantitative images. This approach has been widely used by neuropsychologists.[26] Blood flow maps are acquired during a selected control task and during a test task, which imposes a small and well-defined additional cognitive burden on the brain. Differences in CBF patterns observed between the

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two tasks can then be attributed to neuronal activation and the synaptic activity required to service the additional cognitive burden of the test task[27]. While this process of *cognitive subtraction* has occasionally been criticized,[28 29] it (or one of its variants) still forms the basis of most functional imaging studies. This technique can be extended to studies of drug effects on the brain, where the cognitive burden is invariant, but images are acquired before and after a drug is administered. As with conventional functional imaging, subtraction images can be submitted to careful statistical analysis to identify significant increases or decreases in CBF or CMRgluc associated with administration of a drug.

Several research groups have attempted to use PET to identify sites of anaesthetic action in the human brain,[30–34] and have provided interesting, though not always concordant results. Alkire and colleagues used ^{18}FDG PET to show that halothane[30] and isoflurane[31] resulted in global reductions in cerebral metabolism, with relatively prominent effects on the basal forebrain structures, thalamus, limbic system, and cerebellum. In contrast, propofol[32] produced more metabolic depression in the cortex than in subcortical structures. However, these data are at odds with a more recent study that used $H_2{}^{15}O$ PET to study changes in CBF during graded propofol anaesthesia.[33] These authors showed global reductions in CBF with relatively prominent effects in the medial thalamus, in addition to specific cortical areas. They also demonstrated a close correlation between midbrain and thalamic blood flow, suggesting concordant changes in arousal systems. Interestingly, in another study, high dose midazolam[34] resulted in CBF reductions in multiple cortical areas, but also selectively reduced thalamic CBF. Specific cortical areas that were commonly affected by both agents across three studies included the angular gyrus, anterior cingulate area, and parietal and temporal association cortices, areas that are commonly implicated in arousal and information processing. While it is tempting to suggest that these data reveal the anatomical sites at which propofol exerts its anaesthetic effects, it is also possible that these changes are a consequence of the anaesthetic state produced by propofol acting at a more strategic and focused site.

The functional imaging studies described thus far address the 'where' of anaesthetic action in neuroanatomical terms, but it may be possible to provide additional specificity in terms of the receptor systems involved. Data regarding the regional distribution of receptor subtypes are available from post-mortem and PET ligand studies. Synthesis of such data with changes in regional CBF or CMRgluc would allow us to correlate the distribution of a putative site of anaesthetic action with the documented distribution of regional pharmacodynamic effects.

The paper by Alkire and colleagues[35] in this issue of the journal attempts to do this by using PET data that has, in large part, been previously published by these authors. They relate the cerebral metabolic effects of isoflurane and propofol in human subjects (measured using ^{18}FDG PET)[31 32] to the regional distribution of selected neurotransmitter systems in the brain (using literature data from post-mortem immunohistochemistry[36 37] to define receptor densities). In principle, the approach is a valid one, and has produced interesting results, with dissociation demonstrated between patterns of metabolic suppression seen with propofol and isoflurane. The authors also demonstrate a correlation of regional metabolic suppression by propofol with historical data on regional [^{3}H]diazepam and [^{3}H]flunitrazepam binding. Unexpectedly, isoflurane induced reductions in CMRgluc did not correlate with benzodiazepine binding, but showed an inverse correlation with muscarinic receptor density. These data led the authors to conclude that 'the most logical interpretation for this effect is to suggest that the diazepam binding site on the $GABA_A$ complex is likely to be strongly regionally co-localized with the GABAergic site that mediates propofol's *in vivo* effects on brain metabolism'. They suggest that the absence of such a correlation with isoflurane may be because of a variety of factors, including the possibility that it acts on several receptor systems, and to use common parlance, is a 'dirtier' agent. They suggest that the inverse correlation seen with muscarinic receptor binding can be accounted for by the well documented arousal effects of this receptor system, which would antagonize the metabolic suppression produced by isoflurane in proportion to its local density.

While these data are interesting, several caveats need to be voiced regarding the details of the methodology used for functional imaging studies of anaesthetic action in general, and the current paper in particular. These techniques are based on the assumption that coupled increases in blood flow and glucose metabolism can provide a marker of regional neuronal activation. While this may be true for physiological activation, its relevance to pharmacological deactivation remains unclear. In particular, caution needs to be exercised regarding the implicit but central assumption that a reduction in regional brain metabolism by a drug is necessarily the consequence of a modulation of synaptic activity by the agent *in that region*. While this may well be the case, this is not always so, as suppression of strategic neuronal pathways can clearly affect metabolic activity in their projection areas. For example, marked suppression of thalamic transmission of somatosensory inputs can decrease cortical activity in the somatosensory cortex. Indeed, Angel and colleagues[8] have shown that such thalamic activity is an important site of action for several anaesthetic agents, including those thought to act primarily at the $GABA_A$ complex. These electrophysiological data are concordant with the fMRI data from Antognini[22] who demonstrated lack of cortical somatosensory activation following anaesthesia despite preserved thalamic activation, implying arrest of inputs at a thalamic 'gate'.[22 38] In this situation, the visible deactivation is in the cortex, but the site of anaesthetic action is the thalamus.

The direct vascular effects of anaesthetics present us with another confounder in such studies, especially when the paradigm involves higher doses of halogenated volatile agents.[39] The varying degrees of direct cerebral vasodilation observed with these agents may modulate the CBF responses to activation and deactivation. However, available evidence suggests that even drugs that alter neurovascular coupling do not alter changes in cerebral glucose metabolism, other than by direct neuronal effects.[40]

Studies also need to take account of the variability in functional neuroanatomy between subjects. While these considerations may not be relevant to studies addressing gross patterns of activation and deactivation, they may be important when testing the effects of low or residual levels of anaesthesia in functional imaging paradigms that assess effects on complex cognitive tasks. In these circumstances, functional images should be coregistered to each individual subject's anatomy (using a high resolution MRI), and image averaging undertaken after 'normalizing' these images to a generic template. Ideally, regions of interest that define neuroanatomical structures should be identified on such high-resolution images.

Finally, the source of data for receptor densities in comparisons of the kind used by Alkire and colleagues[35] remains a difficult issue. There are problems using *in vitro* data on [^{3}H]diazepam binding[36] as a basis for assessing regional GABA receptor density. Diazepam binds to both neuronal (GABA/Cl$^-$ channel associated) and mitochondrial benzodiazepine receptors (MBRs).[41] MBRs are typically expressed by inflammatory cells, including activated microglia and blood derived macrophages. Their use of flunitrazepam binding to corroborate these data substantially addresses this criticism, as this is a selective neuronal benzodiazepine ligand.[37] However, regardless of ligand used, post-mortem data cannot account for inter-individual variability, and an ideal study would have compared regional benzodiazepine receptor density in volunteers with regional reductions in ^{18}FDG uptake induced by anaesthetic agents *in the same subjects*. This is a technically feasible exercise, since [^{11}C]flumazenil is a well-characterized PET ligand in humans.[42]

Even if we accept that post-mortem benzodiazepine binding provides an acceptable approximation of central benzodiazepine receptor distribution, caution is required in equating this to GABA$_A$ receptor distribution or to the regional metabolic effects of potentiating GABAergic receptors. Several papers[43 44] (including that by Braestrup and colleagues[36]) make the point that regional [^{3}H]diazepam binding does not necessarily correlate with GABA receptor distribution (though there is a correlation with bicuculline binding sites). More importantly, administration of GABA agonists such as muscimol and THIP (and diazepam) to animals does not produce changes in glucose metabolism in patterns that correlate to receptor density.[43 44]

Despite these reservations, the authors' findings are intriguing. The relative selectivity of propofol induced cortical metabolic suppression (in contrast to that produced by isoflurane, which was more global) may well be caused by variations in the regional density of receptor systems. However, the data provided do not prove this (and to be fair, the authors do not claim it). What the authors have done is to provide a clear experimental basis for an interesting and testable hypothesis. Using modern PET cameras, it should be possible to obtain ^{18}FDG studies at baseline and with anaesthetics, [^{11}C]flumazenil PET images and anatomical MR, for coregistration in a cohort of volunteers with an acceptable radiation burden (≈6 mSv) to participants. Indeed, modern PET ligand technology already offers, or promises to provide, access to a wide variety of receptors[45] (including opioid[46–48] and cholinergic[49–51]) that would be of interest in this context. Future results from such studies promise to be of great interest.

D. K. Menon
Professor of Anaesthesia, University of Cambridge
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References

1 Van Swinderen B, Shook DR, Ebert RH, *et al.* Quantitative trait loci controlling halothane sensitivity in *Caenorhabditis elegans. Proc Natl Acad Sci USA* 1997; **94**: 8232–7

2 Krasowski MD, Koltchine VV, Rick CE, *et al.* Propofol and other intravenous anesthetics have sites of action on the γ-aminobutyric acid type A receptor distinct from that for isoflurane. *Mol Pharmacol* 1998; **53**: 530–8

3 Franks NP, Lieb WR. Selectivity of general anesthetics: a new dimension. *Nat Med* 1997; **3**: 377–8

4 Lees G. Molecular mechanisms of anaesthesia: light at the end of the channel? *Br J Anaesth* 1998; **81**: 491–3

5 Franks NP, Lieb WR. Which molecular targets are most relevant to general anaesthesia? *Toxicol Lett* 1998; **100-101**: 1–8

6 Delia Belelli R, Pistis M, Peters JA, Lambert JJ. General anaesthetic action at transmitter-gated inhibitory amino acid receptors. *Tr Pharmacol Sci* 1999; **20**: 496–502

7 Drummond JC. Monitoring depth of anesthesia. *Anesthesiology* 2000; **93**: 876–82

8 Angel A. Central neuronal pathways and the process of anaesthesia. *Br J Anaesth* 1993; **71**: 148–63

9 Smythies J. The functional neuroanatomy of awareness: with a focus on the role of various anatomical systems in the control of intermodal attention. *Consc Cognit* 1997; **6**: 455–81

10 Simos PG, Papanicolaou AC, Breier JI, *et al.* Insights into brain function and neural plasticity using magnetic source imaging. *J Clin Neurophysiol* 2000; **17**: 143–62

11 Alberstone CD, Skirboll SL, Benzel EC, *et al.* Magnetic source imaging and brain surgery: presurgical and intraoperative planning in 26 patients. *J Neurosurg* 2000; **92**: 79–90

12 Hodes JE, Soncrant TT, Larson DM, Carlson SG, Rapoport SI. Selective changes in local cerebral glucose utilization induced by phenobarbital in the rat. *Anesthesiology* 1985; **63**: 633–9

13 Maekawa T, Tommasino C, Shapiro HM, Keifer-Goodman J, Kohlenberger RW. Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. *Anesthesiology* 1986; **65**: 144–51

14 Ori C, Dam M, Pizzolato G, Battistin L, Giron G. Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. *Anesthesiology* 1986; **65**: 152–6

15 Dam M, Ori C, Pizzolato G, *et al.* The effects of propofol anesthesia on local cerebral glucose utilization in the rat. *Anesthesiology* 1990; **73**: 499–505

16 Lenz C, Rebel A, van Ackern K, Kuschinsky W, Waschke KF. Local cerebral blood flow, local cerebral glucose utilization, and flow-metabolism coupling during sevoflurane versus isoflurane anesthesia in rats. *Anesthesiology* 1998; **89**: 1480–8

17 Cavazzuti M, Porro CA, Biral GP, Benassi C, Barbieri GC. Ketamine effects on local cerebral blood flow and metabolism in the rat. *J Cereb Blood Flow Metab* 1987; **7**: 806–11

18 Burdett NG, Menon DK, Carpenter TA, Jones JG, Hall LD. Visualisation of changes in regional cerebral blood flow (rCBF) produced by ketamine using long TE gradient-echo sequences: preliminary results. *Magn Reson Imag* 1995; **13**: 549–53

19 Howseman AM, Bowtell RW. Functional magnetic resonance imaging: imaging techniques and contrast mechanisms. *Phil Trans Biol Sci* 1999; **354**: 1179–94

20 Ugurbil K, Chen W, Zhu X-H, Kim S-G, Georgopoulos A. Functional mapping in the human brain using high magnetic fields. *Phil Trans: Biol Sci* 1999; **354**: 1195–213

21 Hansen TD, Warner DS, Todd MM, Vust LJ. The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: evidence for persistent flow-metabolism coupling. *J Cereb Blood Flow Metab* 1989; **9**: 323–8

22 Antognini JF, Buonocore MH, Disbrow EA, Carstens E. Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. *Life Sci* 1997; **61**: PL349–54

23 Saha GB, MacIntyre WJ, Go RT. Radiopharmaceuticals for brain imaging. *Semin Nucl Med* 1994; **24**: 324–49

24 Hoffman JM, Coleman RE. Perfusion quantitation using positron emission tomography. *Invest Radiol* 1992; **27**: S22–6

25 Jones T. The role of positron emission tomography within the spectrum of medical imaging. *Eur J Nucl Med* 1996; **23**: 207–11

26 Frackowiak RS, Friston KJ. Functional neuroanatomy of the human brain: positron emission tomography – a new neuroanatomical technique. *J Anat* 1994; **184**: 211–25

27 Jueptner M, Weiller C. Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *Neuroimage* 1995; **2**: 148–56

28 Friston KJ, Price CJ, Fletcher P, Moore C, Frackowiak RS, Dolan RJ. The trouble with cognitive subtraction. *Neuroimage* 1996; **4**: 97–104

29 Price CJ, Friston RJ. Cognitive conjunction: a new approach to brain activation experiments. *Neuroimage* 1997; **5**: 261–70

30 Alkire MT, Pomfrett CJ, Haier RJ, *et al.* Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. *Anesthesiology* 1999; **90**: 701–9

31 Alkire MT, Haier RJ, Shah NK, Anderson CT. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. *Anesthesiology* 1997; **86**: 549–57

32 Alkire MT, Haier RJ, Barker SJ, *et al.* Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. *Anesthesiology* 1995; **82**: 393–403

33 Fiset P, Paus T, Daloze T, *et al.* *Brain* mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J Neurosci* 1999; **19**: 5506–13

34 Veselis RA, Reinsel RA, Beattie BJ, *et al.* Midazolam changes cerebral blood flow in discrete brain regions: an $H_2(^{15})O$ positron emission tomography study. *Anesthesiology* 1997; **87**: 1106–17

35 Alkire MT, Haier RJ. Correlating *in vivo* anaesthetic effects with *ex-vivo* receptor density supports a GABAergic mechanism of action for propofol, but not for isoflurane. *Br J Anaesthesia* 2001; **86**: 618–26

36 Braestrup C, Albrechtsen R, Squires RF. High densities of benzodiazepine receptors in human cortical areas. *Nature* 1977; **269**: 702–4

37 Zezula J, Cortes R, Probst A, Placacios JM. Benzodiazepine receptor sites in the human brain: Autoradiographic mapping. *Neuroscience* 1988; **25**: 771–95

38 Alkire MT, Haier RJ, Fallon JH. Toward a unified theory of narcosis: Brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. *Consc Cognit* 2000; **9**: 370–86

39 Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. *Anesthesiology* 1999; **91**: 677–80

40 Tsukada H, Kakiuchi T, Ando I, Shizuno H, Nakanishi S, Ouchi Y. Regulation of cerebral blood flow response to somatosensory stimulation through the cholinergic system: a positron emission tomography study in unanesthetized monkeys. *Brain Res* 1997; **749**: 10–7

41 Parola AL, Yamamura HI, Laird HE 3rd. Peripheral-type benzodiazepine receptors. *Life Sci* 1993; **52**: 1329–42

42 Frey KA, Holthoff VA, Koeppe RA, *et al.* Parametric *in vivo* imaging of benzodiazepine receptor distribution in human brain. *Ann Neurol* 1991; **30**: 663–72

43 Ableitner A, Herz A. Influence of meprobamate and phenobarbital upon local cerebral glucose utilization: parallelism with effects of the anxiolytic diazepam. *Brain Res* 1987; **403**: 82–8

44 Kelly PA, McCulloch J. Effects of the putative GABAergic agonists, muscimol and THIP, upon local cerebral glucose utilisation. *J Neurochem* 1982; **39**: 613–24

45 Duncan JS. Positron emission tomography receptor studies. *Adv Neurol* 1999; **79**: 893–9

46 Jones AK, Kitchen ND, Watabe H, *et al.* Measurement of changes in opioid receptor binding *in vivo* trigeminal neuralgic pain using [^{11}C]diprenorphine and positron emission tomography. *J Cereb Blood Flow Metab* 1999; **19**: 803–8

47 Casey KL, Svensson P, Morrow TJ, *et al.* Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* 2000; **84**: 525–33

48 Zubieta JK, Dannals RF, Frost JJ. Gender and age influences on human brain mu-opioid receptors by PET. *Am J Psychiatr* 1999; **156**: 842–8

49 Yoshida T, Kuwabara Y, Sasaki M, *et al.* Sex-related differences in the muscarinic acetylcholinergic receptor human brain – a positron emission tomography study. *Ann Nucl Med* 2000; **14**: 97–101

50 Zubieta JK, Koeppe RA, Mulholland GK, Kuhl DE, Frey KA. Quantification of muscarinic cholinergic receptors with [^{11}C]NMPB and positron emission tomography: method development and differentiation of tracer delivery from receptor binding. *J Cereb Blood Flow Metab* 1998; **18**: 619–31

51 Grunwald F, Biersack HJ, Kuschinsky W. Nicotine receptor mapping. *Eur J Nucl Med* 1996; **23**: 1012–4

Editorial II

How can we improve the outcome of oesophagectomy?

Approximately 2000 oesophagectomies are performed in England each year with a 30-day mortality of between 9.5 and 10.5%.[1] Most surgeons that perform oesophagectomies within the UK have a practice of fewer than 40 patients per year, many less than 20 patients per year. This then is a low volume but high-risk operation. Long term survival after surgery for oesophageal cancer remains gloomy with fewer than 25% of patients surviving for 5 yr.[2 3] There is a need to identify perioperative factors implicated in a poor post-operative outcome so those patients vulnerable to complications can be targeted for more intensive monitoring and treatment. In order to provide sufficient patient numbers for analysis, most studies of perioperative risk for oesophagectomy have been performed on retrospective data acquired over several years. It is widely recognized that pulmonary complications following oesophagectomy are associated with patient death, either as a primary condition or secondary to complications such as cardiovascular disorders or sepsis, and so post-operative pulmonary complications are viewed as a legitimate surrogate marker for outcome. Tandon and colleagues,[4] in this issue of the *British Journal of Anaesthesia*, have used retrospective data from an oesophageal cancer database established within their unit and anaesthetic charts to determine perioperative factors associated with acute lung injury, and more particularly adult respiratory distress syndrome, following oesophagectomy for cancer. In doing this they have advanced our understanding of the operative risks. They have reconfirmed some known risks and identified others, some of which are particularly relevant to the anaesthetic management of oesophagectomy patients.

Within the UK, large centres have reported their hospital mortality as between 5 and 8.8%,[2 3 5 6] all below the 10% national average and leading to a supposition that centres, or individuals, with a lower volume of cases may have increased the average by their poorer results. Dalrymple-Hay and colleagues[2] gave weight to this supposition by noting an improvement in the in-hospital mortality of a single surgeon over time. Three studies using the American Medicare database,[7] the Surveillance, Epidemiology and End Results (SEER)–Medicare linked database[8] and the Californian Office of Statewide Health Planning and Development figures[9] confirm that it is the volume of oesophagectomies performed in a centre and, hence, its experience with this operation, not the size of a hospital or its specialization in cancer surgery, that affects patient outcome. Two of these studies,[8 9] determined that hospitals with six or more oesophagectomies per year had a 30-day mortality of between 3.4 and 4.8%, compared with 16 and 17.3% in hospitals with five or fewer. However, higher volume centres also had very variable results, the hospitals that performed more than six oesophagectomies each year had 30-day mortality figures between 0 and 14%,[8] indicating factors other than the hospital volume contribute to outcome. Tandon and colleagues[4] identified that the experience of the surgeon was associated with a reduction in the development of acute lung injury post-operatively. The impact of the surgeon's experience has been measured in factors including reduced single-lung operating time and reduced blood loss.[10] The impact from the concurrent increasing experience of the acute care team, anaesthetists, intensive care doctors, nurses, physiotherapists, etc., and their contribution by improvements in the management of the patient before, during, and after the operation, is not easily quantifiable, although is probably also important. What is evident is that it is those centres, surgeons, and teams with the most experience of oesophageal surgery, not the size or type of hospital, that achieve the best results following oesophagectomy and that oesophageal surgery should be concentrated in tertiary referral centres.

There are three conditions that are implicated in early post-oesophagectomy death that might be influenced by anaesthetic management; pulmonary disorders, anastomotic breakdown, and cardiovascular disease.

Pulmonary disorders

Combined data, mostly from retrospective studies, suggests that approximately 25% of patients suffer from post-operative pulmonary complications following oesophagectomy.[11 12] Retrospective studies rely on clinical detection and recording, and may underestimate the true incidence. A prospective study by Crozier and colleagues[13] of 20 oesophagectomy patients reported post-operative pulmonary complications, as diagnosed by a temperature greater than 38°C on post-operative day 1, and radiographic evidence of pulmonary infiltrates, in 50% of patients. Post-operative mortality or respiratory problems have been associated with pre-operative pulmonary dysfunction,[14 15] reduced vital capacity,[16] and a history of smoking.[4] To date there has been little investigation of operative factors that may be implicated in post-operative pulmonary complications. Tandon and colleagues[4] in their analysis of 146 patients have now linked post-operative adult respiratory distress syndrome to an operative hypoxaemia index, that is the amount of hypoxaemia during one-lung ventilation, standardized for time during one-lung ventilation. This is an important finding as hypoxaemia during one-lung ventilation is very much in the province of anaesthetic management. It is upper gastrointestinal surgeons that undertake most oesophageal surgery in the UK, possibly 80%,[1] and in centres with low numbers of oesophagectomies the anaesthetic management falls mostly to those with little regular practice of one-lung anaesthesia, unless they are also thoracic anaesthetists. Deficiencies in the management of double lumen tubes during one-lung anaesthesia for oesophageal operations were highlighted in the 1996/1997 Report of the National Confidential Enquiry into Perioperative Deaths.[1] This noted, in particular, deficiencies in the recognition and management of badly positioned tubes, and in the prompt and appropriate management of hypoxaemia. What then constitutes sufficient frequency of use of one-lung ventilation to gain proficiency in the technique? Even the most experienced thoracic anaesthetists continue to have problems with double lumen tube positioning. There is also a need to keep up to date with investigations into appropriate ventilation strategies for one-lung ventilation, for example the use of pressure controlled ventilation[17] and 'best' positive end expiratory pressure.[18] Having gained proficiency in one-lung ventilation, what frequency of use is required to maintain it? There is no answer to this other than opinion, but surely, it should be counted in the number of double lumen tubes used per week, not the number per month or year. Those with an infrequent use of double lumen tubes need to review their competency and consider ways in which they can increase their experience. Alternatively, should anaesthetists with infrequent use of double lumen tubes avoid their use during oesophagectomy operations and place more reliance on lung retraction? Again, there is little information. It could be expected that two-lung ventilation in those with an open chest would produce ventilation/perfusion mismatch and severe pulmonary shunt, with most ventilation going to the non-dependant lung and most perfusion to the dependant lung. However, Tachibana and colleagues[19] compared one-lung ventilation with two-lung ventilation in 30 patients undergoing transthoracic oesophagectomy and found greater pulmonary shunting in those having one-lung ventilation. Presumably, during two-lung ventilation lung retraction compensated for the mismatch by directing a proportion of ventilation to the unretracted dependant lung. Tsui and colleagues[20] in a study of 42 oesophagectomy patients found that two-lung high frequency positive pressure ventilation produced fewer severe hypoxic episodes (defined as a Sa_{O_2} <80% at a FI_{O_2} of 1.0) and lower peak and mean airway pressures when compared with one-lung ventilation. There is clearly a need for further investigations into ventilation strategies during oesophagectomy operations.

Anastomotic leaks

Anastomotic leaks after oesophagectomy are reported in 10–15% of cases[11 12] and are implicated in mediastinitis, systemic sepsis, adult respiratory distress syndrome, and death. However, diagnosis is primarily on clinical recognition and some leaks may not be detected. Tanomkiat and Galassi[21] in a prospective radiological study of 114 patients who had undergone oesophageal surgery found anastomotic leaks in 32% of cases. Ischaemia has been shown to occur in the gastric tube during oesophagectomy operations,[22 23] and is believed to contribute to anastomotic leak. Studies on pre-operative optimization in patients undergoing major surgery have shown that by managing the circulation to increase cardiac output, outcome can be improved.[24 25] Would pre-operative optimization or perhaps more intensive operative monitoring and circulatory control, reduce ischaemia in the gastric tube, prevent anastomotic leaks, and improve outcome? The nearest we have to an answer is from Kusano and colleagues[26] who undertook an observational study of oxygen delivery in 115 patients undergoing oesophagectomy. They found that oxygen delivery and consumption measured at 6 h post-operatively was higher in survivors than non-survivors, although not different on or after post-operative day 1. Moreover, oxygen delivery was lower at 6 h after operation in those patients who developed either an anastomotic leak or severe pneumonia.

Cardiovascular complications

Cardiovascular complications, including myocardial infarction and dysrhythmia, have been reported in approximately 11% of patients following oesophagectomy[12] and are implicated in adverse outcome. There is little direct information on the incidence of myocardial ischaemia in patients undergoing oesophagectomy. However, we know from Groves and colleagues[27] that a similar group, those patients undergoing thoracotomy, had a 24% incidence of post-operative myocardial ischaemia and that myocardial ischaemia was associated with adverse outcome. There is some information on dysrhythmia. A prospective study by Ritchie and colleagues[28] noted up to 60% of patients developed cardiac dysrhythmia after oesophagectomy that was not affected by prophylactic digitalization. Amar and colleagues[29] reported that 13% of patients developed supraventricular tachycardia (heart rates between 135 and 180 beats min^{-1}) after oesophagectomy and that supraventricular tachycardia was associated with higher intensive care unit admission rate, longer hospital stay, and a higher 30-day mortality. Mangano and colleagues[30] assessed the effects of atenolol given on the morning of surgery and on subsequent post-operative days for a maximum of 7 days, to patients with a history of ischaemic heart disease or those with two or more risk factors for ischaemic heart disease undergoing all types of non-cardiac surgery. They showed a reduction in mortality and in the incidence of cardiovascular complications, mainly because of a reduction in cardiac deaths over the first 6–8 months. Detailed perioperative assessment of myocardial ischaemia and the effects of strategies for myocardial protection in those patients undergoing oesophagectomy are areas that deserve closer investigation.

Although current mortality and morbidity figures following oesophagectomy are high, there is good reason to hope for improvement, particularly if oesophageal surgery is concentrated in large volume centres. Centres concentrating on oesophageal surgery offer the opportunity to develop greater team experience and to pursue research into management strategies that may improve outcome after oesophagectomy.

Kathleen M. Sherry
Department of Anaesthetics
Northern General Hospital NHS Trust
Herries Road
Sheffield S5 7AU
UK

References

1 The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997. London: NCEPOD, 1998

2 Dalrymple-Hay MJ, Evans KB, Lea RE. Oesophagectomy for carcinoma of the oesophagus and oesophagogastric junction. *Eur J Cardiothorac Surg* 1999; **15**: 626–30

3 Alexiou C, Beggs D, Salama FD, Brackenbury ET, Morgan WE. Surgery for esophageal cancer in elderly patients: the view from Nottingham. *J Thorac Cardiovasc Surg* 1998; **116**: 545–53

4 Tandon S, Batchelor A, Bullock R, *et al.* Peri-operative risk factors for acute lung injury following elective oesophagectomy. *Br J Anaesth* 2001; **86**: 633–8

5 Sabanathan S, Shah R, Tsiamis A, Richardson J. Oesophagectomy in the elderly high-risk patients: role of effective regional analgesia and early mobilisation. *J Cardiovasc Surg* 1999; **40**: 153–6

6 Craig SR, Walker WS, Cameron EW, Wightman AJ. A prospective randomized study comparing stapled with handsewn oesophagogastric anastomoses. *J Coll Surg Edinb* 1996; **41**: 17–19

7 Swisher SG, Deford L, Merriman KW, et al. Effects of operative volume on morbidity, mortality and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2000; **119**: 1126–32

8 Begg CB, Cramer LD, Hoskins WJ, Brennan ME. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA* 1998; **280**: 1747–51

9 Patti MG, Corvera CU, Glascow RE, Way LW. A hospital's annual rate of esophagectomy influences the operative mortality rate. *J Gastrointest Surg* 1998; **2**: 491–2

10 Sutton DN, Wayman J, Griffin SM. Learning curve for oesophageal cancer surgery. *Br J Surg* 1998; **85**: 1399–402

11 Müller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77**: 845–57

12 Rindani R, Martin CJ, Cox MR. Transhiatal versus Ivor Lewis oesophagectomy: is there a difference? *Aust N Z J Surg* 1999; **69**: 187–94

13 Crozier TA, Sydow M, Siewert JR, Braun U. Postoperative pulmonary complication rate and long-term changes in respiratory function following esophagectomy with esophagogastrostomy. *Acta Anaesthesiol Scand* 1992; **36**: 10–5

14 Kuwano H, Sumiyoshi K, Kitamura K, et al. Relationship between preoperative assessment of organ function and postoperative morbidity in patients with oesophageal cancer. *Eur J Surg* 1998; **164**: 581–6

15 Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. *Br J Surg* 1998; **85**: 840–4

16 Nagawa H, Kobori O, Muto T. Prediction of pulmonary complications after transthoracic oesophagectomy. *Br J Surg* 1994; **81**: 860–2

17 Tugrul M, Camci E, Karadeniz H, Senturk M, Pembeci K, Akpir K. Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia. *Br J Anaesth* 1997; **79**: 306–10

18 Inomata S, Nishikawa T, Saito S, Kihara S. 'Best' PEEP during one-lung ventilation. *Br J Anaesth* 1997; **78**: 754–6

19 Tachibana M, Abe S, Tabara H, *et al.* One-lung or two-lung ventilation during transthoracic oesophagectomy? *Can J Anaesth* 1994; **41**: 710–5

20 Tsui SL, Chan CS, Chan AS, Wong SJ, Lam CS, Jones RD. A comparison of two-lung high frequency positive pressure ventilation and one-lung ventilation plus 5 cm H_2O non-ventilated lung CPAP, in patients undergoing anaesthesia for oesophagectomy. *Anaesth Intens Care* 1991; **19**: 205–12

21 Tanomkiat W, Galassi W. Barium sulphate as contrast medium for evaluation of postoperative anastomotic leaks. *Acta Radiol* 2000; **41**: 482–5

22 Boyle NH, Pearce A, Hunter D, Owen WJ, Mason RC. Intraoperative scanning laser Dopler flowmetry in the assessment of gastric tube perfusion during esophageal resection. *J Am Coll Surg* 1999; **188**: 498–502

23 Cooper GJ, Sherry KM, Thorpe JAC. Changes in gastric tissue oxygenation during mobilisation for oesophageal replacement. *Eur J Cardiothorac Surg* 1995; **9**: 158–60

24 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993; **270**: 2699–707

25 Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of perioperative optimisation of oxygen delivery. *BMJ* 1999; **318**: 1099–103

26 Kusano C, Baba M, Takao S, *et al.* Oxygen delivery as a factor in the development of fatal postoperative complications after oesophagectomy. *Br J Surg* 1997; **84**: 252–7

27 Groves J, Edwards ND, Carr B, Sherry KM. Perioperative myocardial ischaemia, heart rate and arrhythmia in patients undergoing thoracotomy: an observational study. *Br J Anaesth* 1999; **83**: 850–4

28 Ritchie AJ, Whiteside M, Tolan M, McGuigan JA. Cardiac dysrhythmia in total oesophagectomy. A prospective study. *Eur J Cardiothorac Surg* 1993; **7**: 420–2

29 Amar D, Burt ME, Bains MS, Leung DH. Symptomatic tachydysrhythmias after esophagectomy: incidence and outcome measures. *Ann Thorac Surg* 1996; **61**: 1506–9

30 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996; **335**: 1713–20

Editorial III

Development of the concept of a liquid pulmonary alveolar lining layer

A remarkable phenomenon has occurred in recent years in pulmonary physiology that may tell us something about the survival of orthodoxy despite ever more aggressive peer review. We refer to the widespread persistence of the notion that the pulmonary alveoli are normally lined with liquid. This notion persists in the scientific community in the face of a simple law of physics that shows it to be impossible. The law, appreciable by schoolchildren who blow soap bubbles, is that the only stable liquid–gas interface has the shape of a sphere, unless gravity upsets things badly. As a pulmonary alveolus is not a spherical structure, its epithelium cannot support a continuous thin lining with liquid that follows the non-spherical contour of its surface. It requires some explanation, therefore, why both the specialist medical literature, and school and university biology and physiology texts, are dominated by the view that the 'alveolar surface is lined with liquid, which forms an air–liquid interface with alveolar gas'.[1] To physicists this is inconceivable.[2]

The story reads like a detective case. In 1929, von Neergaard introduced the idea that surface forces contribute substantially to a tendency for the lungs to collapse, as inflation of excised lungs with liquid (which abolishes any surface facing gas) requires much lower pressures than inflation with gas.[3] In 1957, Mead and colleagues took things further, performing not only inflations but also deflations of excised lungs.[4] They observed that, for a given lung volume, pressure during inflation with gas was higher than during deflation, a phenomenon called pressure–volume hysteresis. The hysteresis largely disappeared during inflation with liquid.

The discovery by Brown and colleagues in 1959, that extracts from lung display a surface tension–area hysteresis on a Langmuir trough that looks a bit like the pressure–volume hysteresis seen in excised lungs,[5] set the scene for an assumption that the alveoli themselves constitute a trough of liquid, albeit one with a complicated geometry. This assumption has pervaded the literature on lung mechanics for over 40 yr, and established itself firmly. Respiratory physiology texts speak with one voice about the liquid lining of the lung, assuming, or explicitly stating, that the whole alveolar surface is covered with a liquid.[1 6–12]

Early on it was appreciated that there was a problem with the assumption that liquid coats the alveolar epithelium. Even if one conceded, for the sake of simplicity, that individual alveoli could be regarded as spherical structures, then the connection of alveoli of different sizes presented a problem, unless the liquid that lines one alveolus was made to stop at an unwetted patch where the alveolus was connected to any neighbouring alveolus. The reason for this is explicitly presented in many textbooks of respiratory physiology.[6 7 9 12] If two model spherical alveoli of *different* radii of curvature (r) are connected together, and an attempt is made to hold a liquid lining in both inflated by the same pressure (p), this proves to be impossible unless the surface tension (T) differs in the two alveoli. Laplace's equation $p=2T/r$ must be obeyed in each alveolus. You cannot change just r whilst T and p stay constant. The texts use this proof to support a separate idea. Studies of surfactant spread on a liquid surface have shown that T tends to increase with the area of the surface. Thus, conveniently, we can imagine that within a single alveolus, T can increase with r. The texts emphasize that, if T can increase with r, then p ($\sim T/r$) can be the same for both alveoli. What the authors do not draw attention to is that T can differ in neighbouring alveoli only if their liquid linings are not connected by a common surface.

This appears to have been clear in 1961 to Clements and colleagues in their seminal paper[13] on 'pulmonary surface tension and alveolar stability' where a model of stability of the alveoli required the assumption that 'the individual units were taken to act independently of one another'. In other words, different alveoli were permitted to have different surface tensions and different pressures across their liquid surfaces, and therefore, not be interconnected by a continuous lining of liquid. Yet this paper is remembered not for this vital aspect of its discussion section, but for its recognition of the possible physiological importance of the observation alluded to above, that lung extracts spread over a trough of liquid display a surface tension that increases with the area to which the surface is expanded. This idea spread, and with it, inappropriately, seems to have spread the postulated liquid lining layer, from one 'independent' model spherical alveolus to the whole network of millions, in violation of the authors' apparent original intentions.

All seemed settled for a while. 'The alveoli have concave surfaces lined with liquid.'[10] The high surface tension of water in contact with air (70 mN m^{-1}) was reduced to something manageable by the presence on the water–air surface of surfactant,[14] the absence of which was responsible for collapse, oedema, and the generation of the distinctive histological finding of hyaline membranes in premature infants dying of what we now call infant respiratory distress syndrome.[15] Dissident scientific voices[16 17] were infrequent and unheeded by the writers of textbooks. Even before university, generations of school advanced biology students continued to be primed think that 'the walls of the alveoli are covered with a thin layer of liquid',[18] not least because it is widely maintained without justification that 'the respiratory surface must be moist, because gases cannot diffuse across it unless they are dissolved in fluid'.[19]

The literature that supports a liquid lining for the lung by considering the stability of neighbouring alveoli of different sizes is the strongest argument *against* it. The reason is that, if *neighbouring* alveoli of different radii of curvature cannot be joined by a shared liquid surface, then neither can neighbouring segments of a *single* alveolus. A stable film of liquid cannot connect two or more regions of an alveolar surface of different radii of curvature whilst maintaining the shape of those surfaces. The argument from Laplace's law shows that a continuous liquid surface within a complex polygonal structure is unstable. This conclusion is consistent with studies of lung histology under electron microscopy in the presence of normal[20] and excess[21] volumes of liquid in the alveoli, in which liquid collections always exhibit a surface that forms part of a sphere, and are separated from each other by segments of epithelium on the surface of which liquid cannot be demonstrated. The assumption made recently by Bastacky and colleagues,[22] that a continuous lining layer of the alveolus revealed by low-temperature scanning electron microscopy consists of 'liquid', is not a consequence of their observations; the layer would be unstable if it were a liquid layer, for the reasons given above. It is beginning to look as if particular care is needed in the use of the word 'liquid', if the nature of the alveolar surface is to be clarified with precision.

The most vociferous opponent of alveolar wetness has made two fundamental errors in his otherwise challenging critique of established dogma.[23] The first is the claim that a hydrophobic surface is required to prevent water from spreading within a polygonal structure. In fact, according to our earlier reasoning, even a hydrophilic surface can only sustain a continuous liquid lining if a sufficient volume of liquid is present on that surface to immerse irregularities beneath a spherical liquid–gas interface. This phenomenon is demonstrated in the micrographs of protein-rich pulmonary oedema published by Bachofen and colleagues.[21] Hills' second error, uncorrected even in a publication well after extensive new findings in the field,[24] is the claim that passive forces alone account for the absorption of liquid from the corners of alveoli. His model of the 'corner pump', in which a liquid globule presents a convex surface to alveolar gas, and is emptied into lung interstitium by surface tension raising the pressure within the globule above that of alveolar gas and interstitial liquid, contrasts strikingly with the model that arises from the work of Basset and colleagues.[25 26] In this model of adult lung, type II epithelial pneumocytes (the ones that secrete surfactant on to the alveolar surface) utilize fuel (ATP) actively to pump sodium, and with it glucose and water, from any collections of water that bathe the apical surface of the cells, into the interstitium.[27] Matthay and colleagues have extensively characterized this process of liquid absorption in animals and humans,[28] and there is some evidence that without active sodium transport fatal alveolar flooding would occur.[29] Interestingly, however, the presence of aquaporins (water transport channels) in alveolar epithelium makes no measurable contribution to recovery from a wide variety of forms of lung injury associated with alveolar oedema.[30]

If the detectives on the case appear to be reluctant to make use of this fascinating new evidence of vigorous transport activity down in the alveoli, they appear even more reluctant to incorporate the most remarkable claims emanating from the laboratory of Scarpelli,[31] who offers a whole 'new anatomy' of the alveolar surface. On the basis of studies that are claimed to preserve surface structures destroyed by the customary methods of histological preparation, Scarpelli has proposed that the alveolar ducts are normally filled with foam surfactant, within which each alveolus can be identified as a separate and complete bubble. Thus, astonishingly, the gas within each alveolus is not free to flow by convection, at least not continuously throughout the whole of the respiratory cycle as has been normally supposed. In this model, the entrances to alveoli are spanned by extremely thin bilayers of surfactant that are presumed usually to contain no 'hypophase' liquid, and consequently take the form of 'Newtonian black films'. Scarpelli's model interestingly emphasizes the movement of 'hypophase liquid . . . from regions of larger radii to those of smaller radii of curvature' (Scarpelli,[31] page 499), and thus indirectly, that much of the alveolar surface, and many of the black films spanning the alveolar entrances, must be devoid of liquid for the reasons discussed earlier in this article. On reading the almost gladiatorial contest between Hills and Scarpelli recently convened in the editorial pages of the *Journal of Applied Physiology*,[32] one would be forgiven for missing the substantial similarities between their models of the alveolus with regard to the necessary absence of liquid from much of the epithelial surface.

A picture clearly emerges that needs to be projected into the less specialized basic scientific and clinical literature. The alveolar surface carries very little liquid, in the usual sense of something that readily flows in response to a pressure gradient. Where liquid has been demonstrated, it lies in isolated collections that are commonly partially submerging type II pneumocytes. These cells appear to be as busy actively emptying the puddles of liquid that bathe them as they are in reducing the surface tension of these puddles by secreting surfactant into them. The larger areas of alveolar surface that are normally unwetted sustain a tension that is imparted on them by neighbouring wetted regions. Wetted and unwetted areas pull gently at each other like competing teams in a tug of war at what the physicists call a 'triple point'. Thus, the alveolar surface can be regarded as having a tension that von Neergaard was able to abolish by inflating the lung with a liquid, even though that surface is not normally entirely wetted. The type II pneumocyte polices alveolar tension over the wider unwetted alveolar epithelium by keeping tension low in the wetted surface within its immediate proximity. Surfactant spreads over wet and unwetted areas alike to provide Bastacky and colleagues' 'thin and continuous' lining layer[22] so strikingly revealed by their low temperature microscopy. The jury remains undecided about whether Scarpelli's foam[31] is a feature more of neonatal lung than adult lung.

A fuller understanding of alveolar mechanics will require more careful attention to the use of terms like *wet*, *moist*, *dry*, *liquid*, and *solid* when applied to this environment. More consideration needs to be given to the important observation of Bangham and colleagues that modest compression of surfactant on water (as in expiration) can generate a solid film that impedes movement within the surface,[33] has the potential structurally to resist alveolar collapse, and, on re-expansion (as in inspiration), may break down into a myriad of planar regions of alternate solid and liquid reminiscent of Arctic pack-ice. The observation of hysteresis in the lung in the 1950s was an early warning that a time-dependent *viscous* behaviour of the alveolar surface would need to be modelled. Virtually no appreciation of the large literature on *viscoelasticity* has been brought to bear on understanding the role of surfactant in the alveolar epithelial lining. Characteristically, biological materials display time-dependent behaviour that can be thought of as showing features of both solids and liquids.[34] The presence of such behaviour in a surface film undergoing repeated stretching may lead to gradients in surface tension and consequently to slow flows in the film that would not otherwise occur.[35] Moreover, repeated stretching of the alveolar epithelium occurs not only with the cycle of breathing; the passage of every red blood cell, as it squeezes through a pulmonary capillary, generates a rapidly alternating curvature of the epithelial surface that has been predicted to assist absorption of alveolar liquid because of the way this deformation of the shape of the surface interacts with the hysteresis of surfactant.[36] We can anticipate that a fuller understanding of the alveolar surface will incorporate a much more dynamic model of surfactant activity; the concept of a trough of water that has no time-dependent properties is no longer sustainable. Walters, in reviewing the role of surfactant in transepithelial movement of liquid, warns: "the movements of water molecules, ions and other solutes in such a thin complex environment are unlikely to obey the laws governing their mobility in more conventional spaces and terms such as 'dry' and 'wet' applied to this microlayer would require philosophical definition".[37] If we can lay to rest the glaring widespread misconception that a layer of liquid, in the sense in which that word is commonly used, can exist on the whole of the normal alveolar surface, we shall be in a better position to make progress. The phenomenal success of the clinical use of surfactant replacement therapy is now well ahead of our understanding of how it works.[38] Furthermore, as intensivists increasingly interest themselves in filling the lung with liquid in order to ventilate it less traumatically, it will be helpful to be clear about when it is wet and when it is dry.[39]

K. L. Dorrington
University Laboratory of Physiology
Parks Road
Oxford OX1 3PT
UK
J. D. Young
Nuffield Department of Anaesthetics
Radcliffe Infirmary
Woodstock Road
Oxford OX2 6HE
UK

References

1 Leff AR, Schumacher, PT. *Respiratory Physiology*. Philadephia: Saunders, 1993
2 Hunter RJ. *Introduction to Modern Colloid Science*. Oxford: Oxford University Press, 1993
3 Von Neergaard K. Neue Auffassungen über einen Grundbegriff der Atemmechanik. *Z Ges Exp Med* 1929; **66**: 373–94
4 Mead J, Whittenberger JL, Radford EP. Surface tension as a factor in pulmonary volume–pressure hysteresis. *J Appl Physiol* 1957; **10**: 191–6
5 Brown ES, Johnson RP, Clements JA. Pulmonary surface tension. *J Appl Physiol* 1959; **14**: 717–20
6 Mines AH. *Respiratory Physiology*, 3rd edn. New York: Raven Press, 1993
7 West JB. *Respiratory Physiology: the Essentials*, 6th edn. Baltimore: Williams & Wilkins, 2000
8 Prange HD. *Respiratory Physiology. Understanding Gas Exchange*. New York: Chapman & Hall, 1996
9 Hlastala MP, Berger AJ. *Physiology of Respiration*. Oxford: Oxford University Press, 1996
10 Widdicombe J, Davies A. *Respiratory Physiology*, 2nd edn. London: Edward Arnold, 1991
11 Staub NC. *Basic Respiratory Physiology*. New York: Churchill Livingstone, 1991
12 Lumb AB. *Nunn's Applied Respiratory Physiology*, 5th edn. Oxford: Butterworth Heinemann, 2000
13 Clements JA, Hulstead RF, Johnson RP, Gribetz I. Pulmonary surface tension and alveolar stability. *J Appl Physiol* 1961; **16**: 444–50
14 Brown ES. Isolation and assay of dipalmityl lecithin in lung extracts. *Am J Physiol* 1964; **207**: 402–6
15 Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959; **97**: 517–22
16 Brooks RE. Lung surfactant: an alternative hypothesis. *Am Rev Resp Dis* 1971; **104**: 585–6
17 Hills BA. *The Biology of Lung Surfactant*. Cambridge: Cambridge University Press, 1981
18 Jones M, Jones G. *Advanced Biology*. Cambridge: Cambridge University Press, 1997
19 Starr C, McMillan B. *Human Biology*, 3rd edn. London: Wadsworth, 1999
20 Gil J, Weibel ER. Improvements in demonstration of lining layer of lung alveoli by electron microscopy. *Respir Physiol* 1970; **8**: 13–26
21 Bachofen H, Schürch S, Michel RP, Weibel ER. Experimental

hydrostatic pulmonary edema in rabbit lungs. *Am Rev Respir Dis* 1993; **147**: 989–96

22 Bastacky J, Lee CYC, Goerke J, *et al.* Alveolar lining layer is thin and continuous: low-temperature scanning microscopy of rat lung. *J Appl Physiol* 1995; **79**: 1615–28

23 Hills BE. The role of lung surfactant. *Br J Anaesth* 1990; **65**: 13–29

24 Hills BE. An alternative view of the role(s) of surfactant and the alveolar model. *J Appl Physiol* 1999; **87**: 1567–83

25 Basset G, Crone C, Saumon G. Significance of active ion transport in transalveolar water absorption: a study on isolated rat lung. *J Physiol* 1987; **384**: 311–24

26 Basset G, Crone C, Saumon G. Fluid absorption by rat lung *in situ*: pathways for sodium entry in the luminal membrane of alveolar epithelium. *J Physiol* 1987; **384**: 325–45

27 Dorrington KL, Boyd CAR. Active transport in the alveolar epithelium of the adult lung:vestigial or vital? *Respir Physiol* 1995; **100**: 177–83

28 Matthay MA, Flori HR, Conner ER, Ware LB. Alveolar epithelial fluid transport: basic mechanisms and clinical relevance. *Proc Assoc Am Physicians* 1998; **110**: 496–505

29 Vejlstrup NG, Boyd CAR, Dorrington KL. Effect of lung inflation on active and passive liquid clearance from *in vivo* rabbit lung. *Am J Physiol* 1994; **267**: L482–7

30 Song Y, Fukuda N, Bai C, Ma T, Matthay MA, Verkman AS. Role of aquaporins in alveolar fluid clearance in neonatal and adult lung, and in oedema formation following acute lung injury: studies in transgenic aquaporin null mice. *J Physiol* 2000; **525**: 771–9

31 Scarpelli EM. The alveolar surface network: a new anatomy and its physiological significance. *Anat Rec* 1998; **251**: 491–527

32 Scarpelli EM, Hills BA. Opposing views on the alveolar surface, alveolar models, and the role of surfactant. *J Appl Physiol* 2000; **89**: 408–12

33 Bangham AD, Morley CJ, Phillips MC. The physical properties of an effective lung surfactant. *Biochim Biophys Acta* 1979; **573**: 552–6

34 Dorrington KL. The theory of viscoelasticity in biomaterials. In: Vincent JFV, Currey JD, eds. *The Mechanical Properties of Biological Materials.* Cambridge: Cambridge University Press, 1980; 289–314

35 Epinosa FF, Kamm RD. Thin layer flows due to surface tension gradients over a membrane undergoing nonuniform periodic strain. *Ann Biomed Eng* 1997; **25**: 913–25

36 Hills BA. Rapidly alternating curvature ('oil canning') as a mechanism preventing alveloar edema. *J Appl Physiol* 1992; **72**: 2108–11

37 Walters D. The role of pulmonary surfactant in transepithelial movement of liquid. In: Robertson B, Van Golde LMG, Batenburg JJ, eds. *Pulmonary Surfactant: from Molecular Biology to Clinical Practice.* Amsterdam: Elsevier Science Publishers, 1992

38 Gibson AT. Surfactant and the neonatal lung. *Br J Hosp Med* 1997; **58**: 381–97

39 Hirschl RB, Conrad S, Kaiser R, *et al.* Partial liquid ventilation in adult patients with ARDS: a multicenter phase I–II trial. Adult PLV Study Group. *Ann Surg* 1998; **228**: 692–700

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CLINICAL INVESTIGATIONS

Correlating *in vivo* anaesthetic effects with *ex vivo* receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane[†] [‡]

M. T. Alkire[1]* and R. J. Haier[2]

[1]Department of Anesthesiology and [2]Department of Pediatrics, University of California-Irvine Medical Center, Orange, California

**Corresponding author: Department of Anesthesiology, University of California, Irvine Medical Center, Route 81A, Bldg 53, 101 City Drive South, Orange, CA 92868, USA*

If the *in vivo* effects of anaesthesia are mediated through a specific receptor system, then a relationship could exist between the regional changes in brain metabolism caused by a particular agent and the underlying regional distribution of the specific receptors affected by that agent. Positron emission tomography data from volunteers studied while unconscious during propofol (n=8) or isoflurane (n=5) anaesthesia were used retrospectively to explore for evidence of relationships between regional anaesthetic effects on brain glucose metabolism and known (*ex vivo*) regional distribution patterns of human receptor binding sites. The regional metabolic reductions caused by propofol differed significantly from those of isoflurane. Propofol's reductions negatively correlated most significantly with the regional distribution of [^{3}H]diazepam and [^{3}H]flunitrazepam (benzodiazepine) binding site densities (r=–0.86, P<0.0005; r=–0.79, P<0.005, respectively) and less strongly with [^{3}H]naloxone (opioid) binding density (r=–0.69, P<0.05). Isoflurane's reductions positively correlated only with muscarinic (acetylcholine) binding density (r=0.85, P<0.05). These findings are consistent with the hypothesis that some of propofol's *in vivo* anaesthetic effects may be mediated through a GABAergic mechanism and suggest some of isoflurane's *in vivo* effects might involve antagonism of central acetylcholine functioning.

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Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian brain. GABA and GABA agonists increase neuronal inhibition by interacting with the post-synaptic GABA$_A$ complex receptor and activating an inhibitory chloride conductance.[1] Increases in the GABAergic transmission results in the inhibition of post-synaptic neuronal functioning. The GABA$_A$ complex receptor is a large post-synaptic transmembrane protein with numerous effector sites.[2] The primary effector site for benzodiazepines is thought to be on the alpha subunit of this protein.[1] It has been suggested that the mechanism of anaesthesia could involve the GABA$_A$ complex receptor.[3–5] In support of the GABA hypothesis is the fact that both i.v. and inhalation anaesthetic agents are known to have *in vitro* effects that modify the functioning of the GABA$_A$ complex.[5–12] In spite of the large literature investigating the *in vitro* actions of anaesthetics on GABA$_A$ complex

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functioning, the importance of each particular agent's *in vitro* GABA agonist activity for ultimately producing the anaesthetic state associated with each particular agent remains to be fully established *in vivo* during anaesthesia.

We postulated that if an anaesthetic agent's mechanism of action involves its GABAergic effects, then a relationship might be demonstrable between the regional cerebral metabolic effects of such an anaesthetic and the known regional distribution of $GABA_A$/benzodiazepine binding sites. Such a relationship, coupled with the known inhibitory nature of the GABA system, would seem to predict that regional brain metabolism should decrease more during anaesthesia in those brain areas which have more receptors.

There are, however, a number of caveats to exploring this idea. First, there is no guarantee that a local decrease in brain metabolism would be secondary to anaesthetic actions within the local area itself. It could be that anaesthetic actions on neurons far removed from the area of interest are the ones actually responsible for the observed local effect. Nonetheless, as GABAergic neurons are generally inhibitory interneurons located within various brain structures, it seems reasonable to expect that a substantial portion of an anaesthetic's effects in any particular structure could be primarily a result of local factors. Second, and conversely, the density of receptors in an area may not determine the local response in that area. It might rather determine a response in some distant area, and the effects in such distant areas could be much larger or smaller in size than the original area of interest. Third, the relationship between regional metabolic reduction during anaesthesia and the various receptor systems involved in producing such effects is likely to be very complex and not well modelled by any attempts at trying to relate metabolic reduction with any single receptor system in isolation. Finally, it remains conceivable that the underlying assumption, regarding regional cerebral metabolic reduction effects during anaesthesia being somehow related to an anaesthetic's effects on a regionally distributed *receptor* system, might be in error. Perhaps a lipid, or gap junction-based model of anaesthesia could better explain the regional cerebral metabolic depressions seen during anaesthesia.

In any event, before undertaking the formal investigation of this receptor-metabolic reduction hypothesis with current brain imaging technology, it would seem prudent to have at least some suggestion of which receptor systems and anaesthetic agents should be examined in order to yield a positive result. Thus, as a first step towards developing the above hypothesis, we retrospectively examined the regional cerebral metabolic depression effects of propofol and isoflurane measured *in vivo* with positron emission tomography (PET) during general anaesthesia and correlated these data with the reported *ex vivo* regional distribution of human benzodiazepine binding sites.[13 14] In addition, to explore the possibility that other cerebral receptor systems may contribute to the regional cerebral metabolic effects of either propofol or isoflurane, we also correlated a number of those other receptor systems with the regional cerebral metabolic effects of both propofol and isoflurane.[15] We chose to use *ex vivo* data for these initial analyses instead of *in vivo* PET data because the *ex vivo* data offers better regional quantification for a number of these ligands of interest.

Methods

The analyses presented in this manuscript are primarily based on cerebral metabolic data previously collected and reported for both propofol and isoflurane anaesthesia.[16 17] However, these data were re-analysed and updated for this report. This report includes regional metabolic data from three subjects not previously reported in the propofol group. Also, this report includes additional regional metabolic data from brain areas not previously reported, such as the caudate and putamen. For both studies Institutional Review Board Committee approval was obtained and all volunteers subsequently gave their written informed consent.

For the propofol study, eight healthy right-handed males each underwent two PET scans; one during a mask general anaesthetic with a propofol infusion, and one while awake. The details of the anaesthetic induction technique and the PET scanning procedures used in this study have been reported previously.[16] Briefly, a propofol infusion technique was used to anaesthetize spontaneously breathing subjects. The infusion was adjusted to the point where each subject just became unresponsive to verbal or tactile stimulation (mean rate=8.8 mg kg^{-1} h^{-1}; mean resultant blood level=3.4 μg ml^{-1} plasma). Regional cerebral glucose metabolism was assessed using the ^{18}fluorodeoxyglucose (FDG) technique. PET scans were done after each FDG uptake period using a NeuroEcat scanner. The PET scanner has a single ring with shadow shields and septa to achieve 7.6-mm resolution (full-width half-maximum) in plane and 9.9 mm resolution in the Z-dimension. For each PET scan session 13 image slices were obtained parallel to the canthomeatal line. Subjects were positioned using laser guidance and scans started at the level of 85% of head height (vertex to canthomeatal line, usually 12–14 cm) and stepped downward in steps of 10 mm.

For the isoflurane study, five healthy right-handed males each underwent two PET scans; one during a mask general anaesthetic with isoflurane and one while awake. The details of the anaesthetic induction technique and the PET scanning procedures used in this study have been reported previously.[17] Briefly, isoflurane was used to anaesthetize spontaneously breathing subjects. The anaesthetic was adjusted to the point where each subject just became unresponsive to verbal or tactile stimulation (mean expired end-tidal concentration=0.5±0.2%, range=0.4–0.9%). Regional cerebral glucose metabolism was again assessed using the FDG technique. The PET scans were done after each FDG uptake period using a newer GE 2048 head-dedicated scanner. Two sets of 15 image planes, resulting in 30 PET images across the whole brain, were obtained per subject. The GE PET scanner has a resolution of 4.5 mm (full-width half-maximum) in plane and 6.0 mm axially. Scans were obtained relative to the canthomeatal line. Subjects were positioned using laser guidance and a thermosetting plastic facemask was used to hold each subject's head stationary during the period of image acquisition. *In vivo* attenuation correction was obtained by prior transmission scanning using a (^{68}Ge/^{68}Ga) rod source.

Glucose metabolic rate (GMR) values (mg 100 g^{-1} min^{-1}) were calculated from scan data using the well-established deoxyglucose kinetic models for autoradiography in animals and modified for humans.[18] Relative GMR (rGMR, defined as GMR within a region of interest divided by whole brain GMR) was used to investigate if the pattern of metabolic changes differed between the two anaesthetic agents studied. rGMR normalizes the global effects of each anaesthetic agent on GMR and allows for direct regional comparisons between agents. An unmatched two-tailed *t*-test was used to evaluate the effects of propofol *versus* isoflurane on the various regions-of-interest examined; a P value <0.05 was considered significant.

Absolute per cent changes in glucose metabolism for the selected brain regions were calculated by comparing the percentage change from the baseline condition to the anaesthetized condition for each region examined. This calculation of absolute metabolic percentage change quantifies the magnitude of the metabolic reduction occurring in each particular brain region-of-interest during anaesthesia and allows for the most direct comparison of the regional percentage change data between the anaesthetics, which were obtained on different PET cameras. For both data sets the scans were transformed into regional glucose metabolic rate values as previously described.[19]

Regions-of-interest, appropriate for each analysis, were selected with a stereotactic method (see Haier and colleagues who shows the region-of-interest templates).[20] Briefly, an automated edge-finding algorithm was used to overlap a template of stereotactically derived region-of-interest boxes (25×25 pi) onto each subject's 2D-PET data slices. Metabolic rates were taken as the average pixel values within the boxes. The slices and various templates were matched in the Z-dimension. Regions that spanned more than one PET slice thickness, such as the thalamus or frontal lobes, were averaged together to obtain a single value for a single subject. The percentage change data for each region were determined for each subject. These values were then averaged together across the subjects to determine the mean regional percentage decrease in absolute glucose metabolism for each particular region with each anaesthetic agent.

The regions selected for the correlation analyses corresponded to the regions-of-interest examined and reported in the literature for the different receptor systems studied. For determination of human benzodiazepine receptor density ([^{3}H]diazepam), the data of Braestrup and colleagues (1977) were used,[13] similar to the analysis performed by Buchsbaum and colleagues.[21] In addition, the more recent benzodiazepine receptor data of Zezula and colleagues (1988) were also examined.[14] These data examined [^{3}H]flunitrazepam binding in the human brain. To obtain a single number for each region of interest within the data of Zezula and colleagues, the values reported for each named area were simply averaged. Thus, for example, even though the hippocampus lists eight separate areas where [^{3}H]flunitrazepam binding was determined, we took the value of the 'hippocampus' to be the average of these eight values. This averaging procedure probably results in a reasonable estimation for the binding sites in each region as it essentially degrades the higher resolution autoradiography sampling to one, which approximates the lower sampling resolution of the PET technique. For determination of GABA ([^{3}H]GABA), acetylcholine (muscarinic antagonist, [^{3}H]quinuclidinyl benzilate), serotonin ([^{3}H]5-hydroxytryptamine), opiate ([^{3}H]naloxone), and beta-adrenergic ([^{3}H]dihydroalprenolol) receptor densities, the data of Enna and colleagues (1977) were used.[15] The percentage of absolute metabolic reduction (from baseline awake to anaesthetized) occurring in each brain region was correlated with the different reported receptor densities using Pearson's r coefficient and Fisher's r to z transform. Percentage change data are plotted as mean (SEM). Regions-of-interest that were too small for the spatial resolution of PET (such as the dentate nucleus or hypothalamus) were not selected from each data set.

Results

The pattern of relative regional cerebral metabolism evident during the anaesthetic state differed significantly between the two agents in a number of different brain regions (Fig. 1). Relative glucose metabolism was significantly higher during isoflurane anaesthesia than during propofol anaesthesia in the temporal ($P<0.001$), parietal ($P<0.001$), and occipital ($P<0.05$) cortical areas. Relative glucose metabolism was significantly higher during propofol anaesthesia than during isoflurane anaesthesia in the basal ganglia ($P<0.0001$), thalamus ($P<0.05$), and midbrain ($P<0.01$). This analysis demonstrates that propofol and isoflurane have a differential effect on regional cerebral metabolism in six of the 10 regions examined. In essence, propofol appeared to be associated with lower relative cortical metabolic rates compared with isoflurane and higher relative subcortical metabolic rates, especially in the basal ganglia.

The two benzodiazepine receptor binding data sets revealed a similar rank ordering of regions between the two studies. In general, the cortex had more receptors than the hippocampus and cerebellum, which had more receptors than the basal ganglia and thalamus, which had more receptors than the pons and white matter. However, the rank ordering between the studies was not identical. Nonetheless, the quantified data from each study correlated highly with

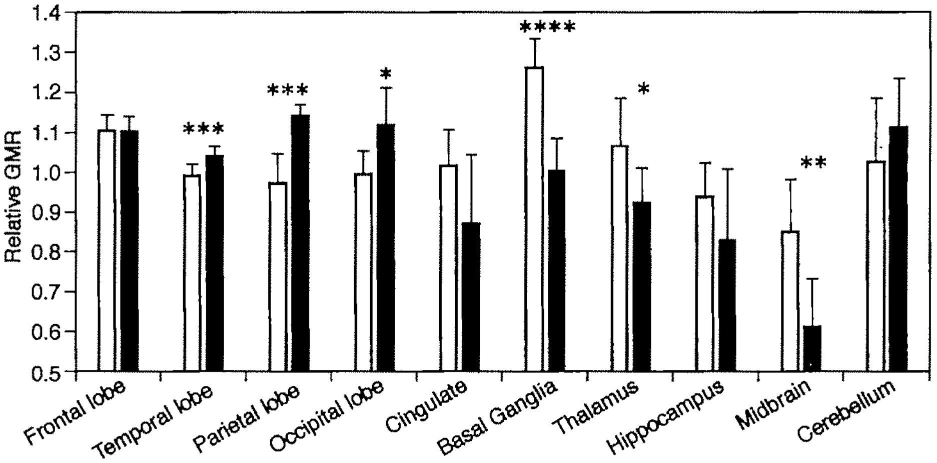

Fig 1 Brain regions where relative glucose metabolic rate values differ significantly between the i.v. anaesthetic agent propofol (n=8), a presumed GABA agonist (white bars) and the inhalation anaesthetic agent isoflurane (n=5; dark bars). Data are mean (SD). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

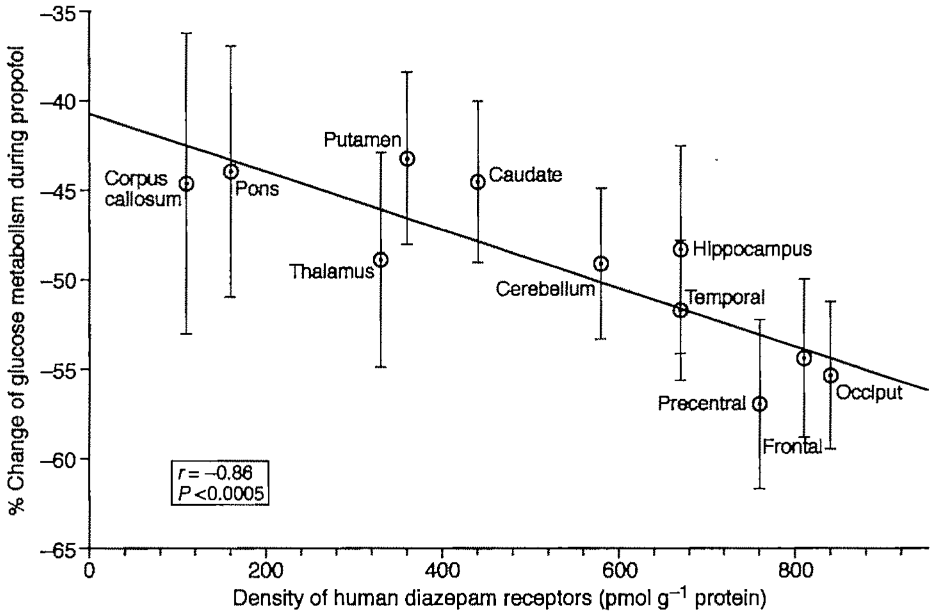

Fig 2 Regression plot showing a significant linear relationship between the regional metabolic reductions occurring during propofol anaesthesia in humans and the known regional benzodiazepine ([^{3}H]diazepam) receptor densities. The figure shows that brain metabolism during propofol anaesthesia decreases more in those brain regions that have more benzodiazepine receptors. The line through the data is the regression line.

the other across the 11 regions examined (r=0.934, P<0.0001; Table 1).

The regional metabolic reductions evident during propofol anaesthesia correlated most significantly with [^{3}H]diazepam receptor density (r=–0.86, P<0.0005; Fig. 2 and Table 2). Propofol's *in vivo* anaesthetic effects also correlated significantly with [^{3}H]flunitrazepam binding sites (r=–0.79, P<0.005; Table 2). The fact that propofol's effects correlated with both sets of benzodiazepine receptor density data is not too surprising given the strong degree of correlation between them.

In contrast, the regional metabolic reductions evident during isoflurane anaesthesia did not correlate significantly with the known distribution of human benzodiazepine receptor densities for either diazepam (Fig. 3) or flunitrazepam (Table 2). Isoflurane's effects did, however, show a positive correlation with muscarinic binding sites (Fig. 4 and Table 2). Because the data are plotted as percentage decreases, it is important to explicitly state that a positive correlation means that brain metabolism during anaesthesia decreases less in those brain regions with more receptors. Conversely, a negative correlation means that brain metabolism during anaesthesia decreases more in those brain regions with more receptors.

Another difference between propofol and isoflurane emerged in the correlation with [^{3}H]naloxone (opioid) binding sites. Propofol's regional effects showed a weak significant negative correlation with naloxone receptors, whereas there was a positive trend to the relationship between those receptors and the effects of isoflurane (Figs 5 and 6).

Table 1 Regional values for benzodiazepine binding densities. Correlation value r=0.93, P<0.001

Brain	[^{3}H]diazepam[13] region (pmol mg protein^{-1})	[^{3}H]flunitrazepam[14] (fmol mg protein^{-1})
Occiput	840	550
Frontal	810	508
Precentral	780	481
Temporal	670	538
Hippocampus	670	528
Cerebellum	580	309
Caudate	440	307
Putamen	360	304
Thalamus	330	343
Pons	160	140
Corpus callosum	110	100

Discussion

These data show that a relationship exists between the regional cerebral metabolic reduction effects of propofol anaesthesia in humans and the underlying regional distribution of human benzodiazepine ([^{3}H]diazepam and [^{3}H]flunitrazepam) receptor densities. The presumed GABA agonist propofol is thought to produce the anaesthetic state by increasing an inhibitory chloride conductance, which is mediated through the GABA$_A$ complex,[10] in a subunit dependent manner.[22] In our data, propofol was found to be inhibitory (i.e. depressed regional cerebral metabolism) in all brain regions examined.[16] As the GABA$_A$ complex is thought to be the effector site for benzodiazepine binding, our findings offer a link between

Table 2 Correlations between regional metabolic effects of propofol and isoflurane anaesthesia with various *ex-vivo* receptor systems. *P<0.05, **P=0.005, ***P<0.0005

Receptor system	(Number of comparable regions)	Propofol (r-value) (n=8)	Isoflurane (r-value) (n=5)
GABA	(9)	−0.29	−0.44
Adrenergic	(9)	+0.05	+0.56
Muscarinic (ACH)	(7)	+0.24	+0.85*
Serotonin	(9)	−0.60	+0.30
Opiate	(9)	−0.69*	+0.52
Diazepam	(11)	−0.86***	-0.11
Flunitrazepam	(11)	−0.79**	−0.003

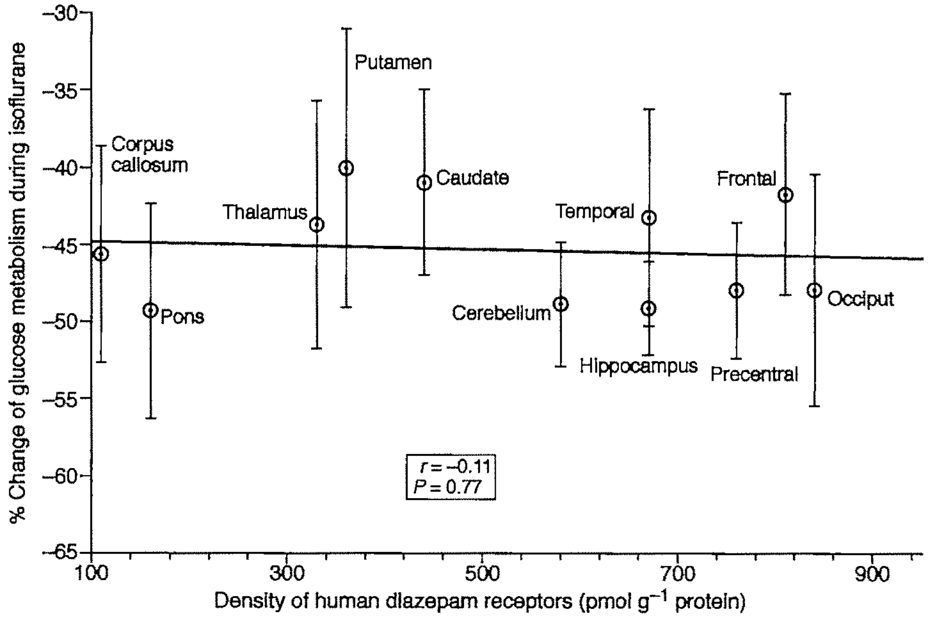

Fig 3 Regression plot showing an apparent lack of a significant relationship between the regional metabolic reductions occurring during isoflurane anaesthesia in humans and the known regional benzodiazepine ([^{3}H]diazepam) receptor densities. These data do not directly support a GABA$_A$ complex mediated mechanism for the production of the anaesthetic state associated with isoflurane.

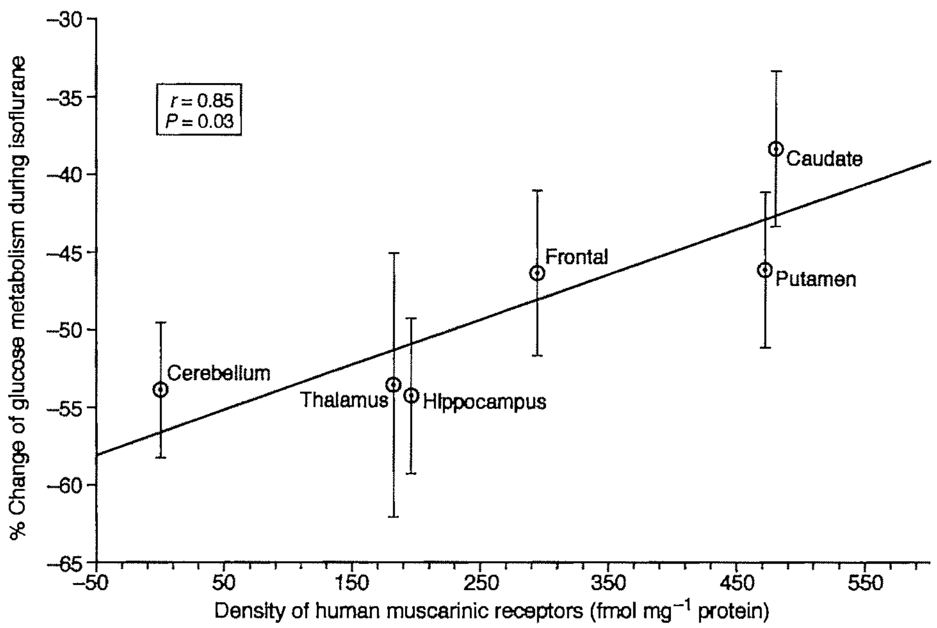

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Fig 4 Regression plot showing a significant relationship between the regional metabolic reductions occurring during isoflurane anaesthesia in humans and the known regional muscarinic acetylcholine ([^{3}H]quinuclidinyl benzilate) receptor densities.

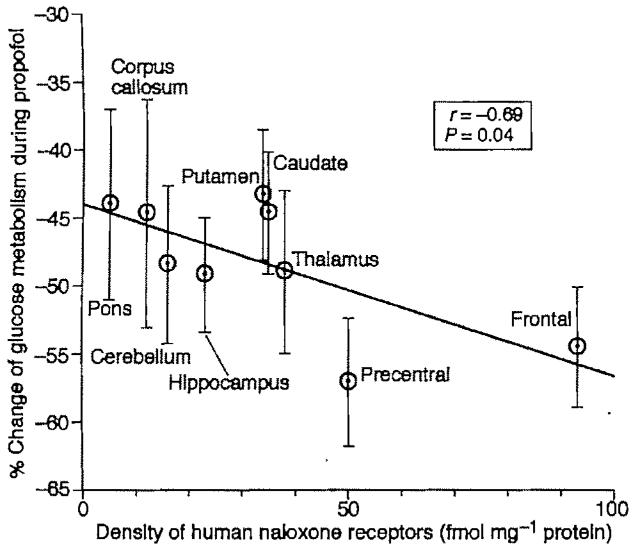

Fig 5 Regression plot showing a significant negative relationship between the regional metabolic reductions occurring during propofol anaesthesia and the known regional opiate ([^{3}H]naloxone) receptor densities.

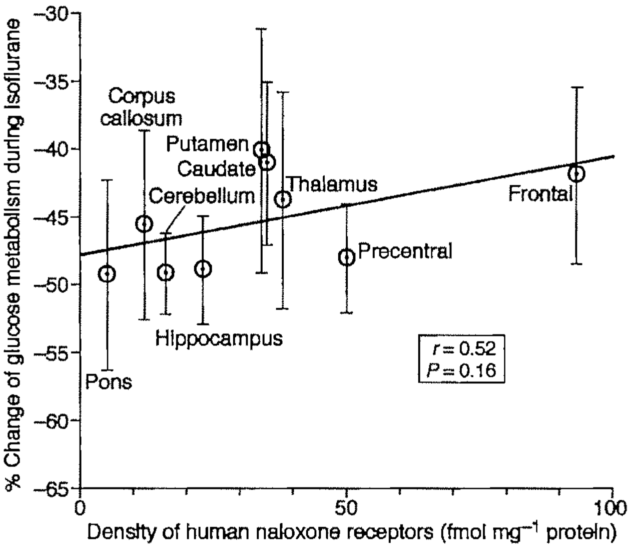

Fig 6 Regression plot showing a positive trend exists between the regional metabolic reductions occurring during isoflurane anaesthesia and the known regional opiate ([^{3}H]naloxone) receptor densities. Note that the direction of the correlation is opposite of that shown for propofol in Figure 5.

the functional metabolic (i.e. anaesthetic) effects of propofol in the human brain with its presumed cellular (i.e. GABA$_A$ complex mediated) mechanism of action. Thus, those brain areas with more benzodiazepine receptors show a greater decrease in regional cerebral metabolism during propofol anaesthesia than do those brain areas with fewer receptors. The most logical interpretation for this effect is to suggest that the benzodiazepine binding site on the GABA$_A$ complex is likely to be strongly regionally co-localized with the GABAergic site that mediates propofol's *in vivo* effects on brain metabolism. Furthermore, as the GABA receptor is only potentiated by propofol if a gamma subunit is present, it would be fair to say that the correlation found between propofol and benzodiazepine receptor densities is with a subset of GABA receptors (N. P. Franks, personal communication). This subset distinction explains why it is possible to have found a correlation with the diazepam and flunitrazepam binding sites without also having found a correlation between propofol's regional effects and GABA receptors, *per se*, as assessed with [^{3}H]GABA binding.

In contrast with the findings with propofol, the pattern of regional cerebral metabolic reductions produced by isoflurane was not at all consistent with a GABAergic mediated mechanism for the production of the anaesthetic state associated with isoflurane. The most obvious interpretation of this finding might be to simply conclude that the *in vivo* regional cerebral metabolic effects of isoflurane are not mediated through a GABAergic mechanism. This would imply that the limited *in vitro* effects isoflurane does have on GABAergic transmission probably do not play a significant role in producing the anaesthetic state associated with isoflurane. However, for a number of reasons (discussed below), including the low statistical power of n=5, and the fact that a correlation reveals nothing about causation, the present findings can not rule out the possibility that a GABAergic mediated mechanism still does underlie the anaesthetic state produced by inhalation anaesthetics (including isoflurane).

Isoflurane may have failed to show a relationship between benzodiazepine ([^{3}H]diazepam or [^{3}H]flunitrazepam) receptor density and regional cerebral metabolic changes, because isoflurane's effects on regional metabolism may simply occur at a molecular site on the benzodiazepine receptor, which is functionally different from that of propofol's. Early evidence for this being a possible explanation of our correlational results appears to be emerging from *in vitro* work using site-directed mutagenesis of human $GABA_A$ receptors. Krasowski and colleagues report that specific mutations can abolish regulation of the $GABA_A$ receptor by isoflurane without affecting propofol mediated receptor interactions.[23] Alternatively, it is possible that isoflurane could act on the same molecular site as does propofol, but isoflurane could inhibit the site *in vivo* in a functionally different manner than does propofol. This 'functionally different manner' might not lead to the same degree of regional metabolic suppression for each region as that seen with propofol. Furthermore, it is possible that isoflurane might act *in vivo* at the same site as does propofol, and in a similar manner to that of propofol, but its effects on regional metabolism might be masked or complicated by its actions within other receptor systems. In other words, the overall effects of isoflurane on regional cerebral metabolism might simply represent a less 'pure' picture of regional metabolic effects/receptor interactions than what was found with propofol, as a prototypical GABA agonist. Therefore, simply because this analysis did not reveal a relationship between the regional metabolic changes produced by isoflurane and regional benzodiazepine binding, one cannot rule out an important role for the $GABA_A$ receptor in the mechanism of isoflurane anaesthesia (i.e. 'absence of evidence is not evidence of absence'). In fact, other functional brain imaging evidence is emerging which suggests that the $GABA_A$ receptor is modulated, at least to some extent, by isoflurane *in vivo*.[24]

The correlation found between isoflurane's effects on regional cerebral metabolism, and the regional distribution of muscarinic acetylcholine receptors was somewhat unexpected, but nonetheless, appears reasonable. The inverse nature of the correlation between muscarinic receptors and the regional cerebral metabolic changes caused by isoflurane anaesthesia suggests that regional cerebral metabolism decreases less in those brain areas during isoflurane anaesthesia, which have more muscarinic receptors. Muscarinic signalling in the central nervous system is known to be intimately involved with regulating level of arousal and consciousness, and cholinergic signalling systems tend to enhance wakefulness.[25] Thus, our findings with isoflurane would seem to imply that brain areas with higher levels of muscarinic receptors are more resistant to the metabolic depressant effects of isoflurane inhalation anaesthesia and may be, in essence, harder to 'anaesthetize' with isoflurane.

Unfortunately, because a unified picture of nicotinic receptor binding data remains lacking in humans, the regional cerebral metabolic changes seen with isoflurane and the regional distribution of nicotinic acetylcholine receptors were not directly compared in the present study. Such a comparison might offer important insights into the mechanism of anaesthesia as the nicotinic acetylcholine receptor has been shown to have binding site properties consistent with a potential target site for general anaesthetic action,[26] and is known to be very sensitive to clinically relevant doses of inhalation agents.[27]

The correlation of propofol with naloxone receptors is interesting and might seem to imply that propofol ought to have some opioid-like activity. However, a more likely explanation of this correlation is to suggest that some degree of regional co-localization can exist between the various receptors examined. For example, the propofol cerebral metabolism changes, also, weakly trended the serotonin receptor sites. This relationship was not completely unexpected as the naloxone and serotonin binding densities were noted to have a strong correlation with each other across the nine comparable regions examined (r=0.76, P<0.005). Additionally, for the propofol naloxone correlation it should be noted that a large part of the correlation is driven by the one value associated with the frontal lobe. Eliminating this one frontal lobe value as an outlier, or examining this relationship with a non-parametric (Kruskal–Wallis) statistical approach reduces the correlation value to a non-significant level (P<0.14). In contrast, using the same non-parametric statistical approach with the benzodiazepine ([^{3}H]diazepam) receptor density data, the correlation with propofol's regional cerebral metabolic reduction effect still remains significant (P=0.038).

Whereas these data do support the importance of propofol's GABAergic effects in producing the anaesthetic state in humans and suggest an involvement of muscarinic signalling with isoflurane anaesthesia, some limitations with the present methodology used in these exploratory analyses need to be considered. Most problematical is the region-of-interest selection. We attempted to match regions as reported historically; however, there is no standard definition of a particular region-of-interest. For example, 'caudate' may mean the whole caudate (including the tail), or just the head of the caudate. We took 'caudate' to mean the head of the caudate as this is a large enough brain structure to obtain a reliable PET signal from. With the requirement for similar assumptions to be made before analysis in each region-of-interest examined, some inaccuracies are likely in the present comparisons.

Additionally, the historical data may contain some element of sampling error. For example, in some cases, with the Braestrup data the values for some regions-of-interest, such as the corpus callosum, represent the measurement of only two subjects.[13] However, this is much less likely a problem for the data of Zezula and colleagues. Their findings were obtained in twenty-one post-mortem brains. They reported only limited variability from case to case; 'This variation was, however, limited and in most areas the standard error of mean (SEM) did not exceed the 10% of the mean densities'.[14] Given the strong correlation between the benzodiazepine binding site density studies, with an r=0.93, it seems unlikely that either investigator was that far off the mark with their *ex vivo* quantification attempts.

Another limitation is that the number of comparable regions for some of the receptor systems, like the muscarinic system, is small. At best, any conclusions regarding a single agent's correlation with a single receptor system must be tempered in caution. Nonetheless, the power of the present exploration does not come from any single correlation rather it comes from the fact that the two different agents were compared using the same, albeit potentially flawed, set of rulers. Thus, the most important findings would seem to be related to those comparisons that show one effect with one agent and a different effect with the other agent. In this sense, the relationship between benzodiazepine binding sites and the regional cerebral metabolic effects of propofol is made more interesting because this type of relationship did not occur with isoflurane. Conversely, the relationship between isoflurane and muscarinic receptors is interesting because it did not occur with the propofol. Furthermore, the relationship of both agents with the opioid receptors becomes interesting because it differs between the two agents. It is positive for propofol and negative for isoflurane. Any ultimate explanation for the mechanism of anaesthesia will have to be able to account for these agent-specific differences in regional cerebral metabolic effects.

Another potential concern for interpreting these data is that we used historical *ex vivo* human data instead of *in vivo* data. *Ex vivo* data may not compare favourably with the real *in vivo* situation for some of the receptors examined. This is less of a concern for the benzodiazepine receptor; however, as the benzodiazepine receptor appears to be quite stable post-mortem[28] and is unaffected by age, gender, post-mortem delay or pre-mortem drug treatment.[14] We avoided the *in vivo* PET data on benzodiazepine binding studies because the semi-quantitative nature of the *in vivo* studies performed to date has produced inconsistent results with only limited areas presented for examination. Nonetheless, many of the receptor systems examined in this study could be examined with PET, *in vivo*. Most importantly, measurement of regional benzodiazepine binding with flumazenil is now quite common. The next logical step in elucidating the relationships suggested in the present study would be to compare benzodiazepine binding sites with propofol's regional cerebral metabolic effects *in vivo* using PET in the same set of volunteers. This would allow for more direct comparisons involving the relationship between cerebral metabolic effects and regional receptor systems without confounds associated with region-of-interest selections.

In summary, given the assumptions required to make the present comparisons, it is notable that a simple linear relationship between benzodiazepine ([^{3}H]diazepam and [^{3}H]flunitrazepam) binding sites and propofol's effects on regional cerebral metabolism would be found. It has been proposed that changes in chloride based neuronal inhibition (mediated through the GABA_A receptor complex) could be the underlying mechanism of general anaesthesia.[4,5] Our findings with propofol are consistent with that hypothesis; however, our findings with isoflurane inhalation anaesthesia suggest that the anaesthetic state caused by isoflurane may involve a more complex mechanism.

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References

1 Schofield PR, Darlison MG, Fujita N, *et al.* Sequence and functional expression of the GABA_A receptor shows a ligand-gated receptor super-family. *Nature* 1987; **328**: 221–7

2 Schofield PR. The GABA_A receptor: molecular biology reveals a complex picture. *Trends Pharmacol Sci* 1989; **10**: 476–8

3 Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature* 1994; **367**: 607–14

4 Cheng SC, Brunner EA. A hypothetical model on the mechanism of anesthesia. *Med Hypotheses* 1987; **23**: 1–9

5 Moody EJ, Suzdak PD, Paul SM, Skolnick P. Modulation of the benzodiazepine/gamma-aminobutyric acid receptor chloride channel complex by inhalation anesthetics. *J Neurochem* 1988; **51**: 1386–93

6 Hall AC, Lieb WR, Franks NP. Stereoselective and non-stereoselective actions of isoflurane on the GABA_A receptor. *Br J Pharmacol* 1994; **112**: 906–10

7 Concas A, Santoro G, Mascia MP, et *al.* The general anesthetic propofol enhances the function of gamma-aminobutyric acid-coupled chloride channel in the rat cerebral cortex. *J Neurochem* 1990; **55**: 2135–8

8 Harris B, Wong G, Skolnick P. Neurochemical actions of

inhalational anesthetics at the $GABA_A$ receptor complex. *J Pharmacol Exp Ther* 1993; **265**: 1392–8

9 Mihic SJ, McQuilkin SJ, Eger EI, 2nd, Ionescu P, Harris RA. Potentiation of gamma-aminobutyric acid type A receptor-mediated chloride currents by novel halogenated compounds correlates with their abilities to induce general anesthesia. *Mol Pharmacol* 1994; **46**: 851–7

10 Orser BA, Wang LY, Pennefather PS, MacDonald JF. Propofol modulates activation and desensitization of $GABA_A$ receptors in cultured murine hippocampal neurons. *J Neurosci* 1994; **14**: 7747–60

11 Peduto VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. *Anesthesiology* 1991; **75**: 1000–9

12 Quinlan JJ, Firestone S, Firestone LL. Isoflurane's enhancement of chloride flux through rat brain gamma-aminobutyric acid type A receptors is stereoselective. *Anesthesiology* 1995; **83**: 611–5

13 Braestrup C, Albrechtsen R, Squires RF. High densities of benzodiazepine receptors in human cortical areas. *Nature* 1977; **269**: 702–4

14 Zezula J, Cortes R, Probst A, Placacios JM. Benzodiazepine receptor sites in the human brain: autoradiographic mapping. *Neuroscience* 1988; **25**: 771–795

15 Enna SJ, Bennett JP, Jr, Bylund DB, *et al.* Neurotransmitter receptor binding: regional distribution in human brain. *J Neurochem* 1977; **28**: 233–6

16 Alkire MT, Haier RJ, Barker SJ, *et al.* Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. *Anesthesiology* 1995; **82**: 393–403

17 Alkire MT, Haier RJ, Shah NK, Anderson CT. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. *Anesthesiology* 1997; **86**: 549–57

18 Phelps ME, Huang SC, Hoffman EJ, *et al.* Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979; **6**: 371–88

19 Buchsbaum MS, DeLisi LE, Holcomb HH, *et al.* Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psych* 1984; **41**: 1159–66

20 Haier RJ, Siegel BV, Jr, MacLachlan A, *et al.* Regional glucose metabolic changes after learning a complex visuospatial/motor task: a positron emission tomographic study. *Brain Res* 1992; **570**: 134–43

21 Buchsbaum MS, Wu J, Haier R, *et al.* Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. *Life Sci* 1987; **40**: 2393–400

22 Mihic SJ, Ye Q, Wick MJ, *et al.* Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. *Nature* 1997; **389**: 385–9

23 Krasowski MD, Koltchine VV, Rick CE, *et al.* Propofol and other intravenous anesthetics have sites of action on the gamma-aminobutyric acid type A receptor distinct from that for isoflurane. *Mol Pharmacol* 1998; **53**: 530–8

24 Gyulai F, Firestone L, Mintun M, *et al.* Dose-dependent effects of isoflurane on GABAa receptor conformation *in vivo* in humans. *Anesthesiology* 1997; **87**: A612

25 Durieux ME. Muscarinic signaling in the central nervous system. Recent developments and anesthetic implications. *Anesthesiology* 1996; **84**: 173–89

26 McKenzie D, Franks NP, Lieb WR. Actions of general anaesthetics on a neuronal nicotinic acetylcholine receptor in isolated identified neurones of Lymnaea stagnalis. *Br J Pharmacol* 1995; **115**: 275–82

27 Violet JM, Downie DL, Nakisa RC, Lieb WR, Franks NP. Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. *Anesthesiology* 1997; **86**: 866–74

28 Whitehouse PJ, Lynch D, Kuhar MJ. Effects of postmortem delay and temperature on neurotransmitter receptor binding in a rat model of the human autopsy process. *J Neurochem* 1984; **43**: 553–559

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Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index

S. B. Fehr[1], M. P. Zalunardo[1], B. Seifert[2], K. M. Rentsch[3], R. G. Rohling[1], T. Pasch[1] and D. R. Spahn[1]*

[1]Institute of Anaesthesiology, University Hospital Zurich, Switzerland. [2]Department of Biostatistics, University of Zurich, Switzerland. [3]Institute for Clinical Chemistry, University Hospital Zurich, Switzerland.

**Corresponding author: Institute of Anaesthesiology, University Hospital, Rämistrasse 100, CH-8091 Zurich, Switzerland*

Assessment of the effect of clonidine on depth of anaesthesia is difficult because clonidine combines analgesic, sedative and direct haemodynamic effects. We thus evaluated the influence of clonidine on the bispectral index (BIS) and its potential dose-sparing effect on propofol. After induction of anaesthesia with target-controlled infusion of propofol and obtaining an unchanged bispectral index (pre-BIS), clonidine 4 μg kg^{-1} or placebo was administered randomly to 50 patients in a double-blind manner. Subsequently, if there was a decrease in BIS we reduced the target concentration of propofol until pre-BIS was reached. The pre-BIS was maintained and a remifentanil infusion was added during surgery. The courses of the BIS, heart rate and blood pressure were recorded and the total amounts of intra-operative propofol and remifentanil were determined. Assessment of implicit memory during anaesthesia was performed with an auditory implicit memory test consisting of item sequences. Administration of clonidine resulted in a decrease in the BIS from 45 (SD 4) to 40 (6) ($P<0.001$), which allowed a reduction of propofol target concentration from 3.3 (0.6) to 2.7 (0.7) μg ml^{-1} ($P<0.001$) and measured propofol concentration from 2.9 (0.6) to 2.5 (0.7) μg ml^{-1} ($P=0.009$) in order to maintain the pre-BIS value. During subsequent surgery, propofol requirements were reduced by 20% ($P=0.002$) in the clonidine group and a similar amount of remifentanil was used in each group. The increase in anaesthetic depth given by clonidine can therefore be measured with bispectral EEG analysis and allows reduction of the propofol dose to achieve a specific depth of anaesthesia.

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Clonidine, a centrally acting α_2-receptor agonist, has attracted increasing interest as an adjunct to anaesthesia. A variety of beneficial effects before, during and after anaesthesia, such as sedation, analgesia, increased cardiovascular stability and improved outcome, have been attributed to clonidine.[1 2] Clonidine reduced the requirement for volatile anaesthetics when assessed by haemodynamic responses.[3 4] Imai found that a reduced dosage of propofol was required after administration of clonidine,[5] whereas Goyagi found a reduced induction but not maintenance dose of propofol when using haemodynamic end-points.[6] However, assessing anaesthetic depth by the use of haemodynamic variables after administration of clonidine, which depresses autonomic nervous system responses, is fraught with difficulties. A lack of tachycardia or hypertension does not necessarily indicate an adequate depth of anaesthesia. Because centrally acting α_2-receptor agonists have effects on the EEG and the bispectral index (BIS) in the awake patient, we thought that the effect of clonidine on depth of anaesthesia might also be monitored using the BIS.[7 8] This study was conducted to evaluate first whether the sedative effect of clonidine is measurable by BIS analysis during propofol anaesthesia, and secondly whether BIS monitoring allows the maintenance of a constant anaesthetic depth despite a reduced propofol dosage after administration of clonidine.

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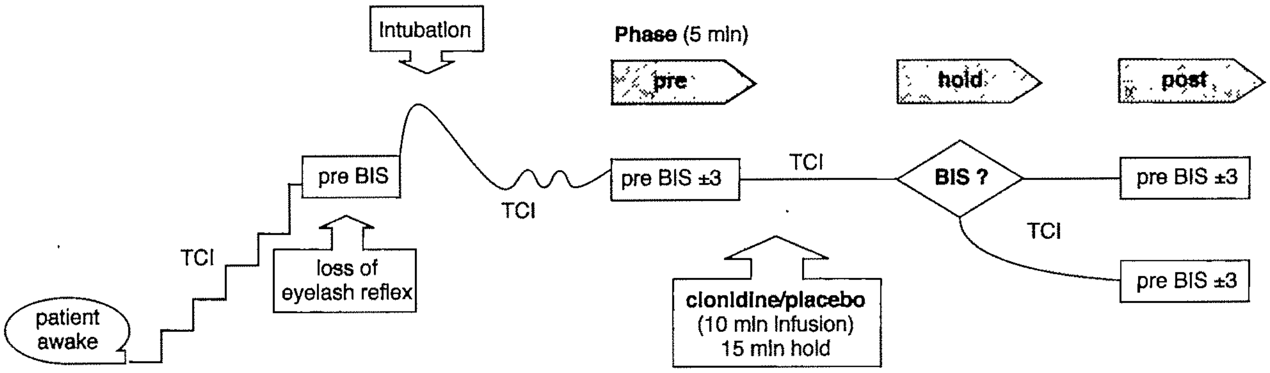


Fig 1 Study design: preoperative examination. BIS?: after clonidine/placebo infusion, the BIS response was evaluated. With an unchanged BIS the target plasma concentration of propofol (TCI) was maintained; when a decrease in the BIS was observed, the target plasma concentration of propofol was reduced until the BIS was again at the pre-BIS level.

Materials and methods

This randomized, double-blind, placebo-controlled study was designed to test the hypothesis that clonidine deepens anaesthesia as measured by the BIS and allows the dose of propofol to be reduced.

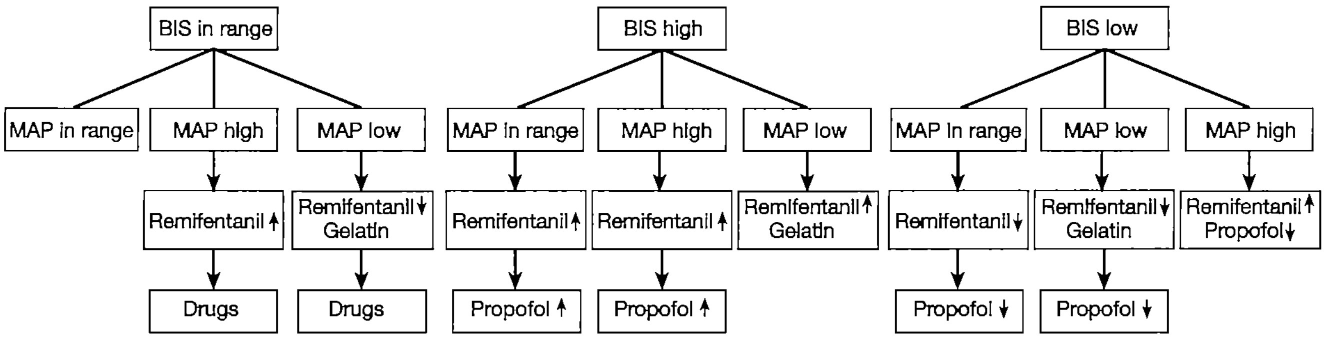
After obtaining institutional review board approval and written informed consent, we studied 50 German-speaking patients, aged 18–70 yr, American Society of Anesthesiologists physical status I or II, scheduled for superficial surgical procedures expected to last at least 45 min. Patients with cardiopulmonary, neuropsychiatric or hearing disorders and patients taking any medication affecting cardiovascular or neurological function were excluded. Patients received no premedication.

After admission of the patients to the operating room, an i.v. cannula was placed and standard monitoring was established. In addition, the level of consciousness was surveyed by bispectral EEG analysis (Aspect A-1000 EEG monitor, software module 3.12; Aspect Medical Systems, Natick, MA, USA) and expressed as the BIS. After preparation of the skin, four disposable, self-prepping, low-impedance electrodes (Zipprep; Aspect Medical Systems) were positioned over the left and right prefrontal cortex (Fp1, Fp2) and referenced to a central vertex electrode (Cz) according to a standard montage. Impedances were kept at less than 5000 Ω.

Anaesthesia was induced by propofol infusion using a target-controlled infusion (TCI) pump (Graseby 3500; Graseby Medical, Watford, UK). The target plasma concentration of propofol (μg ml^{-1}) was raised in incremental steps until the patient became unconscious, as defined by the loss of the eyelash reflex. The corresponding BIS was recorded. To intubate the trachea, anaesthesia was deepened by increasing the target plasma concentration of propofol and muscle paralysis was achieved with rocuronium 0.6 mg kg^{-1}. During the whole procedure, the patients' lungs were ventilated with 40% oxygen in air. The target plasma concentration of propofol was adjusted to achieve a constant level of anaesthesia, indicated by a BIS corresponding to the BIS at loss of eyelash reflex (pre-BIS). The target concentration of propofol was adjusted in steps of 0.1–0.5 μg ml^{-1}. A steady state was assumed only when the calculated effect site concentration equalled the target plasma concentration.

Keeping the propofol target concentration constant, we allocated the patients randomly to receive either an infusion of clonidine 4 μg kg^{-1} or placebo in 0.9% NaCl 100 ml during the following 10 min. If the BIS was altered 15 min after the end of infusion, the target plasma concentration of propofol was reduced until the pre-BIS value was reached (Fig. 1). Heart rate, arterial blood pressure, the BIS and target plasma concentration of propofol were recorded every 2 min. Blood samples for measuring the blood concentration of propofol were taken via an additionally established 14 G cannula in a large vein on the contralateral arm before ('pre' phase) and 15 min after clonidine or placebo infusion ('hold' phase) and after adjusting the propofol target concentration ('post' phase), to achieve a steady state, defined as a constant BIS (= pre-BIS ±3) over a period of at least 5 min. The blood samples (4 ml heparinized tubes) were stored immediately at –20°C and analysed by high-performance liquid chromatography with fluorescence detection.[9]

During the surgery, supplementary analgesia was provided by remifentanil infusion at a rate between 0.01 and 1 μg kg^{-1} min^{-1} to maintain an unchanged BIS and haemodynamic stability (Fig. 2). The target concentration of propofol was maintained unchanged unless the target BIS (pre-BIS ±5) could not be maintained by varying the remifentanil infusion rate, and at the end of the operation to allow a fast wake-up. Heart rate, arterial blood pressure, BIS, propofol target concentration and remifentanil infusion rate were recorded every 5 min during the intra-operative course. Hypertension or hypotension (±20% of the arterial blood pressure in the 'pre' phase) occurring with the BIS in the target range or sudden and marked blood pressure changes were scheduled to be treated with esmolol (20 mg)



Definitions
BIS in range: pre BIS ± 5
MAP high: > 120 mm Hg or pre MAP + > 20%
MAP low: < 50 mm Hg or pre MAP – > 20%
Tachycardia: > 120 beats min^{-1}
Bradycardia: < 40 beats min^{-1}

Dosage
Propofol: 1.5–8 µg ml^{-1}
Remifentanil: 0.01–1 µg kg^{-1} min^{-1}

Treatment of acute haemodynamic events
MAP high: Esmolol 20 mg or Phentolamine 1 mg i.v.
MAP low: Ephedrine 5 mg i.v.
Tachycardia: Esmolol 20mg i.v.
Bradycardia: Atropine 0.5 mg i.v.

Fig 2 Anaesthetic decision tree during the operation.

or phentolamine (1 mg) respectively, ephedrine (5 mg) and gelatin (500 ml). Simultaneously, remifentanil and propofol dosing was adjusted in accordance with the study protocol (Fig. 2). Atropine (0.5 mg) was administered if the heart rate fell below 40 beats min^{-1}. Plasma concentrations of clonidine were analysed from blood samples 15 min ('hold' phase) and 180 min after clonidine infusion and at the end of surgery. Heparinized blood (6 ml) was placed on ice immediately after sampling, centrifuged promptly at +4°C to separate the plasma, and stored at –20°C until analysis by high-performance liquid chromatography. To avoid clonidine redosing, the propofol-sparing efficacy was assessed during the first 180 min after clonidine administration.

To assess implicit memory during anaesthesia, four test items of different categories were presented to the patients through headphones at the following time points: immediately before ('pre' phase), 15 min after ('hold' phase), after possible reduction of propofol ('post' phase) and 180 min after infusion of clonidine (or the end of the operation, whichever came first). The test items were selected in a pilot study in which 48 patients were asked to name 10 items from four categories (animals, fruits, colours, countries). The sequence in which these items were named was recorded and we evaluated which item was named on average in 10th position. These four items, named last in each category, were selected to be presented to the patients in the present study. On the post-operative day, patients in the current study were asked to name 10 items in each category. The sequence in which these items were named was again recorded. Scores of test items (10 points for first position, 9 points for second position,. .. and 0 points for not mentioning the item at all) were computed for each study time point (pre, hold, post and intra-operative) to compare the clonidine and placebo groups.[10] Explicit memory was assessed by asking for any free recall.

Statistical analysis

The duration of the different phases of the intra-operative course and memory test items were analysed using the Mann–Whitney *U*-test and Fisher's exact test. Repeated measures analysis of variance with two within-group factors [phase (pre, hold, post) and repetition (steady state values in each phase)] and one between-group factor (clonidine/placebo) and *post hoc* *t*-test with Bonferroni correction were performed to evaluate differences in the progression of the preoperative phases pre, hold and post. To analyse differences between phases (pre, hold post) within groups (clonidine, placebo), paired *t*-tests with Bonferroni correction were used. Continuous data are presented as mean (SD). *P* values less than 0.05 were considered significant.

Results

The two groups were similar with regard to the physical characteristics of the patients (Table 1) and the type of operation. Times from the end of the preoperative examination to the start of the operation and the duration of operation did not differ between the groups (Table 1).

Pre-operative measurements before and after administration of clonidine

TCI values, BIS, measured propofol blood concentrations, heart rate and mean arterial blood pressure were similar in the two groups before starting the clonidine or placebo infusion in the 'pre' phase (Fig. 3). Fifteen minutes after the infusion (hold phase), haemodynamic variables were still

Table 1 Patient characteristics and operative times. Values are mean (SD) or absolute count. Op. time=duration of operation; SO time=time from end of pre-operative study phase to start of operation; Ext. time=time from end of operation to extubation

	Clonidine (n=25)	Placebo (n=25)
Age (yr)	38 (20–62)	39 (18–65)
Males	10	13
Weight (kg)	69 (13)	75 (14)
Height (m)	1.69 (0.11)	1.71 (0.07)
ASA I	22/25	22/25
ASA II	3/25	3/25
Op. time (min)	130 (70)	138 (83)
SO time (min)	40 (36)	46 (27)
Ext. time (min)	5 (7)	3 (5)

similar between the groups but there was a significant decrease in heart rate in both groups (P<0.001). In the 'hold' phase, the BIS showed a significant decrease in the clonidine group (P<0.001) and was significantly lower than in the placebo group (P=0.002). After achieving pre-BIS in the 'post' phase, the clonidine group showed a significant decrease in the target propofol concentration (P<0.001) and measured blood concentrations of propofol (P=0.009), and a significant decrease in heart rate and mean arterial pressure (MAP) (P=0.002). In the 'post' phase, the target propofol concentration (P=0.002) and the measured propofol blood concentrations (P=0.006) were significantly lower in the clonidine group than in the placebo group, but similar BIS values (P=0.403) (Fig. 3) resulted. The measured plasma concentrations of clonidine were in the therapeutic range ['hold' phase, 2.7 (0.8) ng ml^{-1}; 180 min after clonidine administration or the end of operation, 1.7 (0.5) ng ml^{-1}].

Intra-operative measurements

Throughout the intra-operative course, similar values for the BIS were observed in the two groups. In the clonidine group, this was achieved despite lower propofol target concentrations and a reduced total propofol dosage (Table 2). Interestingly, patients in both groups received similar amounts of remifentanil (Table 2). Despite a significant decrease in mean intra-operative MAP, the patients in the clonidine group needed similar amounts of gelatin, atropine and ephedrine (Table 2). No patient was treated with phentolamine or esmolol. The time to extubation did not differ between the groups (Table 1).

Implicit and explicit memory analysis

There were no differences in age or gender between patients in the pilot study and those in the current study [mean age: pilot group 38 (18–75) yr; current group 38 (18–65) yr; male/female 20/28 *vs* 23/27]. The scores for the presented items were similar between the pilot study and the current study and between the clonidine and the placebo groups at all time points (P>0.05) (Fig. 4). No patient had any free recall either of the presented items or of any other pre- or intra-operative events.

Discussion

Intravenous clonidine results in a decrease in the BIS during propofol anaesthesia and allows reduction of the target concentration of propofol in order to maintain a certain BIS level. The pharmacodynamic effect of clonidine during anaesthesia can thus be monitored with the BIS.

Clonidine affects the EEG in a variety of ways: it increases slow-wave activity (delta) and attenuates the physiological alpha fluctuations.[7] [11] Although no data exist regarding the specific effect of clonidine on the BIS, clonidine causes sedation[12] and therefore may also affect the BIS,[13] which indeed was demonstrated in the present study.

The propofol saving in the current study of nearly 20% is comparable with earlier studies in which an isoflurane saving of approximately 40% was reported.[14] [15] The somewhat greater isoflurane saving in that study may be explained by a different EEG analysis, a larger dose of clonidine (5 *vs* 4 µg kg^{-1}) and perhaps especially because isoflurane dosing was guided mainly by haemodynamic responses. Another trial investigated the effect of clonidine on i.v. anaesthesia with propofol and fentanyl and found a reduction of approximately 40% in the propofol requirement with similar doses of fentanyl after clonidine.[5] Despite similar anaesthetics and a relatively small dose of oral clonidine (150 µg), this study revealed a greater reduction of propofol in comparison with our study. This may be explained by dosing propofol according to arterial blood pressure and heart rate but without any monitoring of brain function, such as the BIS.

Larger doses of clonidine may allow greater reductions in anaesthetic drug use, but may lengthen the time required for recovery from anaesthesia.[6] This was not observed in the present study and the time to extubation was similarly short in the two groups. The restrictive propofol dosing in our control group may be another reason for the relatively small propofol saving compared with previous studies. This might be linked to continuous monitoring of the BIS, which has been reported to facilitate immediate recovery and to decrease the consumption of anaesthetics.[16]

Clonidine administration resulted in a lower propofol requirement for a certain level of anaesthesia to be achieved, as defined by similar BIS values. The fact that no explicit intra-operative awareness occurred and no signs of implicit memory were observed indicates that the anaesthetic state induced by clonidine and low-dose propofol may be similar to the anaesthetic state induced by a larger dose of propofol alone. It is evident that larger trials will be necessary to show conclusively that a lower dose of propofol combined with clonidine is as safe as a larger dose propofol in preventing intra-operative awareness.

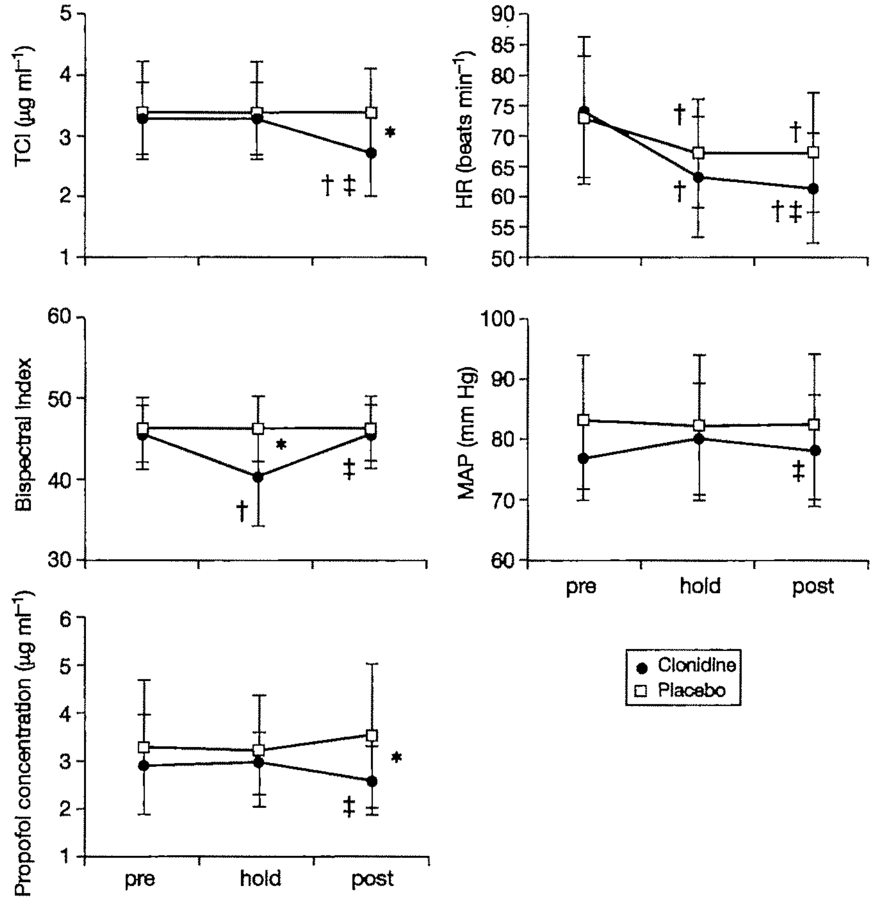


Fig 3 Propofol target plasma concentration (TCI), bispectral index, blood concentration of propofol, heart rate (HR) and mean arterial pressure (MAP) before (pre) and after (hold) clonidine administration and after achieving the pre-BIS-value (post) with possible reduction of propofol in patients treated with i.v. clonidine or placebo (mean±SD). †Significant difference from 'pre' condition (within-group comparison, after Bonferroni correction, $P<0.017$). ‡Significant difference from 'hold' condition (within-group comparison, after Bonferroni correction, $P<0.017$). *Significant difference between groups (after Bonferroni correction, $P<0.017$).

Table 2 Intra-operative BIS, haemodynamic variables, anaesthetic requirements and the use and dose of gelatin, atropine and ephedrine for haemodynamic events. Values are mean (SD), absolute counts or median and range. BIS=bispectral index; HR=heart rate; MAP=mean arterial pressure; Prop=intra-operative propofol infusion rate; Remi=intra-operative remifentanil infusion rate. $P<0.05$ is significant

	Clonidine	**Placebo**	***P* (clonidine *vs* placebo)**
BIS	48 (4)	48 (4)	0.73
HR (beats min^{-1})	53 (5)	54 (7)	0.46
MAP (mm Hg)	71 (7)	78 (9)	**0.01**
Target concentration of propofol (μg ml^{-1})	2.3 (0.4)	2.8 (0.5)	**<0.01**
Prop (mg kg^{-1} min^{-1})	0.11 (0.02)	0.13 (0.02)	**<0.01**
Remi (μg kg^{-1} min^{-1})	0.14 (0.08)	0.11 (0.08)	0.13
Use of gelatin	10/25	10/25	1
Gelatin (ml)	0 (0–1500)	0 (0–1000)	0.48
Use of atropine	5/25	4/25	0.73
Atropine (mg)	0 (0–1.5)	0 (0–1.0)	0.67
Use of ephedrine	4/25	1/25	0.35
Ephedrine (mg)	0 (0–10)	0 (0/5)	0.16

We analysed the propofol concentration of venous blood to avoid the insertion of an arterial catheter or repeated arterial puncture. In addition, we ensured that the time to steady state was always more than 10 min, and thus arterial and venous propofol concentrations should have been stable and in a fixed ratio to each other.[17] Therefore, venous propofol concentrations may be considered representative of the blood concentration

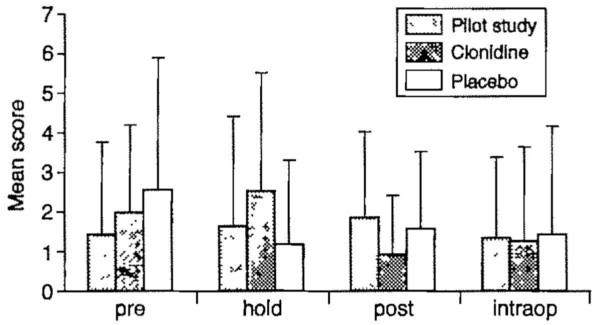


Fig 4 Scores of test items (10 = first position, 1 = 10th position, 0 = not listed) at different time points in the current study (clonidine *vs* placebo) and in the pilot study. There are no significant differences between the groups. Values are mean+SD.

of propofol when comparing different phases and the two groups.

Clonidine did not have any additional effect in reducing the intra-operative requirement for remifentanil. This is in agreement with a study by Engelman and colleagues, describing similar intra-operative opioid requirements with and without clonidine.[18] However, clonidine has been reported to reduce post-operative opioid requirements.[19] Because the primary site of analgesic action of clonidine has been proposed to be the spinal dorsal horn, it is conceivable that systemically administered clonidine has a relatively limited analgesic efficacy, enabling modulation of post-operative pain but being less effective against the more intense intra-operative pain.[20]

In summary, the pharmacodynamic effect of i.v. clonidine can be monitored with the BIS. Intravenous clonidine causes a significant decrease in the BIS and allows a lower propofol dose to be used at a similar level of anaesthesia without intra-operative awareness or prolonged recovery times.

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References

1 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605

2 Stuhmeier KD, Mainzer B, Cierpka J, Sandmann W, Tarnow J. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. *Anesthesiology* 1996; **85**: 706–12

3 Thomson IR, Peterson MD, Hudson RJ. A comparison of clonidine with conventional preanesthetic medication in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1998; **87**: 292–9

4 Howie MB, Hiestand DC, Jopling MW, Romanelli VA, Kelly WB, McSweeney TD. Effect of oral clonidine premedication on anesthetic requirement, hormonal response, hemodynamics, and recovery in coronary artery bypass graft surgery patients. *J Clin Anesth* 1996; **8**: 263–72

5 Imai Y, Mammoto T, Murakami K, *et al.* The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia. *J Clin Anesth* 1998; **10**: 660–5

6 Goyagi T, Tanaka M, Nishikawa T. Oral clonidine premedication reduces induction dose and prolongs awakening time from propofol–nitrous oxide anesthesia. *Can J Anaesth* 1999; **46**: 894–6

7 Bischoff P, Mahlstedt D, Blanc I, Schulte am Esch J. Quantitative topographical electroencephalographic analysis after intravenous clonidine in healthy male volunteers. *Anesth Analg* 1998; **86**: 202–7

8 Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000; **90**: 699–705

9 Knibbe CA, Koster VS, Deneer VH, Stuurman RM, Kuks PF, Lange R. Determination of propofol in low-volume samples by high-performance liquid chromatography with fluorescence detection. *J Chromatogr B Biomed Sci Appl* 1998; **706**: 305–10

10 Graf P, Masson MEJ. *Implicit Memory: New Directions in Cognition, Development, and Neuropsychology.* Hillsdale (NJ): Lawrence Erlbaum, 1993

11 Bischoff P, Scharein E, Schmidt GN, von Knobelsdorff G, Bromm B, Esch JS. Topography of clonidine-induced electroencephalographic changes evaluated by principal component analysis. *Anesthesiology* 2000; **92**: 1545–52

12 Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. *Anesthesiology* 2000; **93**: 1345–9

13 Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000; **93**: 1336–44

14 Gabriel AH, Faryniak B, Sojka G, Czech T, Freye E, Spiss CK. Clonidine: an adjunct in isoflurane N_2O/O_2 relaxant anaesthesia. Effects on EEG power spectra, somatosensory and auditory evoked potentials. *Anaesthesia* 1995; **50**: 290–6

15 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10

16 Song D, Joshi GP, White PF. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. *Anesthesiology* 1997; **87**: 842–8

17 Wang YP, Cheng YJ, Fan SZ, Liu CC. Arteriovenous concentration differences of propofol during and after a stepdown infusion [published erratum appears in *Anesth Analg* 1995; **80**: 434]. *Anesth Analg* 1994; **79**: 1148–50

18 Engelman E, Lipszyc M, Gilbart E, *et al.* Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–87

19 Bernard JM, Hommeril JL, Passuti N, Pinaud M. Postoperative analgesia by intravenous clonidine. *Anesthesiology* 1991; **75**: 577–82

20 Hirata K, Koyama N, Minami T. The effects of clonidine and tizanidine on responses of nociceptive neurons in nucleus ventralis posterolateralis of the cat thalamus. *Anesth Analg* 1995; **81**: 259–64

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Peri-operative risk factors for acute lung injury after elective oesophagectomy[†]

S. Tandon[1], A. Batchelor[1], R. Bullock[1], A. Gascoigne[1], M. Griffin[2], N. Hayes[2], J. Hing[3], I. Shaw[1], I. Warnell[1] and S. V. Baudouin[1 3]*

[1]Departments of Anaesthesia and Intensive Care Medicine, Newcastle upon Tyne NHS Trust, Newcastle upon Tyne, UK. [2]Northern Oesophago-gastric Unit, Newcastle upon Tyne NHS Trust, Newcastle upon Tyne, UK. [3]University Department of Surgical and Reproductive Sciences, University of Newcastle upon Tyne, UK

**Corresponding author: Department of Anaesthesia, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK*

Acute lung injury after oesophagectomy is well recognized but the risk factors associated with its development are poorly defined. We analysed retrospectively the effect of a number of pre-, peri- and post-operative risk factors on the development of lung injury in 168 patients after elective oesophagectomy performed at a single centre. The acute respiratory distress syndrome (ARDS) developed in 14.5% of patients and acute lung injury in 23.8%. Mortality in patients developing ARDS was 50% compared with 3.5% in the remainder. Features associated with the development of ARDS included a low pre-operative body mass index, a history of cigarette smoking, the experience of the surgeon, the duration of both the operation and of one-lung ventilation, and the occurrence of a post-operative anastomotic leak. Peri-operative cardiorespiratory instability (measured by peri-operative hypoxaemia, hypotension, fluid and blood requirements and the need for inotropic support) was also associated with ARDS. Acute lung injury after elective oesophagectomy is associated with intraoperative cardiorespiratory instability.

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A recent confidential enquiry into post-operative mortality and morbidity highlighted the large contribution that respiratory complications make to poor outcome after elective oesophageal surgery.[1] One specific pulmonary disorder, the acute respiratory distress syndrome (ARDS) is associated with oesophagectomy and occurs in 10–20% of cases.[2 3] Diffuse damage to the alveolar epithelial/endothelial interface of the lung increases vascular permeability and impairs pulmonary gas exchange by alveolar flooding and infiltration with acute inflammatory cells. Mortality of ARDS exceeds 50%.[4]

The development of ARDS is associated with systemic inflammatory conditions such as septic shock, major trauma, massive blood transfusion and pancreatitis.[5] Systemic release of circulating inflammatory mediators and the activation of leukocytes may contribute to the lung injury. The cause of ARDS after oesophagectomy is unknown but the release of inflammatory mediators and gut-related endotoxins may contribute.[6] In addition, the period of one-lung anaesthesia required during oesophagectomy may also be important. Collapse and subsequent re-expansion of the non-dependent lung may produce lung injury by an ischaemic/reperfusion mechanism,[7] and over-ventilation of the dependent lung could also produce injury by micro-barotrauma.[8]

Recent reports of preoptimization in high-risk surgical patients suggest another mechanism of lung injury. Preoptimization techniques are used to increase cardiac output deliberately and produce so-called supranormal levels before, during and after surgery.[9] A number of studies have reported decreased mortality and morbidity (including respiratory) after preoptimization.[10] The corollary of these observations would be the finding that morbidity and mortality are increased in non-preoptimized patients who demonstrate cardiorespiratory instability in the peri-operative period.

We therefore studied retrospectively the operative course of a large group of patients who underwent elective

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[†] This article is accompanied by Editorial II.

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oesophagectomy at a single centre. We examined a number of measures of peri-operative cardiorespiratory instability and performed single and multi-variable analysis on the association between these and the development of ARDS, respiratory morbidity and mortality after elective oesophageal surgery.

Methods

One hundred and ninety-three patients were operated on for oesophageal cancer at Newcastle General Hospital and the Royal Victoria Infirmary between January 1, 1996 and December 31, 1999. Of these, five underwent trans-hiatal oesophagectomy, two underwent emergency subtotal oesophagectomy and 17 were found to be inoperable. One hundred and sixty-nine patients underwent conventional two-phase oesophagectomy, consisting of subtotal oesophageal resection with right thoracotomy, oesophagogastrostomy and radical two-field lymph node dissection. We analysed retrospectively 168 patients who underwent elective two-phase resection (the notes of one patient could not be obtained). Two patients developed severe intraoperative haemodynamic compromise that necessitated abandonment of the resection. Data were collected from patient case notes, from our prospectively compiled oesophagectomy database and from the anaesthetic charts. Missing values were recorded as such. Data were divided into pre-operative, peri-operative and post-operative data. The pre-operative data included age, sex, smoking history, history of ischaemic heart disease, body mass index (BMI) (kg m^{-2}), arterial blood gases on air, simple spirometry (forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) as percentage predicted and FEV1/FVC ratio), haemoglobin concentration, liver function (serum bilirubin, albumin, aspartate transaminase), renal function (blood urea and creatinine) and the stage of tumour (TNM classification: stage I, IIA, IIB, III and IV). The stage of tumour was recorded from the post-operative histology.

Intraoperative data included duration of surgery (from skin incision to closure), duration of one-lung ventilation (OLV), a calculated measure of the degree and duration of hypotension during the procedure (the hypotension index; see below), a calculated measure of the degree and duration of oxygen desaturation during OLV (the hypoxaemia index; see below), inotrope requirement (both bolus and infusion), estimated blood loss (ml) and blood transfusion (units), crystalloid infusion (litres), colloid infusion (litres) and the use of epidural analgesia. The experience and grade of the surgeon and anaesthetist were also recorded. All operations were performed by a consultant surgeon. The surgeon and anaesthetist were classified as experienced if they had more than 5 yr of consultant experience in the management of oesophagectomies.[11]

Post-operative data included post-operative blood transfusion, post-operative inotrope use and the occurrence of post-operative anastomotic leak.

Post-operative complications

Information on the occurrence of specific post-operative complications was collected. Acute lung injury (ALI) and ARDS were defined according to the American European Consensus Conference on ARDS criteria.[12] ALI was defined as Pa_{O_2}/FI_{O_2} less than 40 kPa and ARDS as Pa_{O_2}/FI_{O_2} less than 27 kPa. Additional criteria included the presence of bilateral infiltrations on plain chest radiograph, and a pulmonary artery occlusion pressure of less than 18 mm Hg if measured or no clinical evidence of left atrial hypertension. We also defined a group of patients with post-operative respiratory failure on the basis of having ALI and the continuing need for invasive ventilatory support [not CPAP (continuous positive airway pressure) alone] more than 48 h after oesophagectomy. Specific respiratory complications included persistent pleural effusions, prolonged (>7 days) pneumothoraces and hydropneumothoraces, empyema, chylothoraces, pneumonia (fever, purulent sputum, new pulmonary infiltrate and organisms identified), pulmonary emboli, laryngeal oedema and the development of fistulae. In-hospital deaths during the admission for oesophagectomy were also recorded.

Anaesthetic technique

All of the patients in this study were anaesthetized by one of three consultant anaesthetists. When appropriate, premedication was prescribed and patients received their normal medication pre-operatively. Anaesthesia was induced i.v. and maintained with a combination of systemic opiates, neuromuscular paralysis and a volatile anaesthetic agent. Subtotal oesophagectomy is a two-phase procedure, the first phase being a laparotomy conducted in the supine position and the second phase involving a right-sided thoracotomy in the left lateral position. Surgical access in the latter stage necessitates the collapse of the non-dependent lung. To facilitate a period of one-lung anaesthesia, intubation was performed using a left-sided double-lumen Robertshaw endobronchial tube. After intubation, the correct position of the double lumen tube was confirmed by fibre-optic bronchoscopy and patients were ventilated with an Engstrom MIE Carden Ventilator (Engstrom MIE, Exeter, Devon, UK). Initial ventilation settings were adjusted to achieve a tidal volume of 8–10 ml kg^{-1}, a respiratory rate of 10–12 b.p.m., an inspiratory:expiratory (I:E) ratio of 1:2 and an end-tidal carbon dioxide tension of 4–5 kPa. Before the second part of the operation the patient was placed on an FI_{O_2} of 100%, placed in the left lateral decubitus position and OLV was commenced. Ventilator settings were adjusted to maintain tidal volume and end-tidal carbon dioxide at pre-OLV levels. Peak airway pressures invariably increased because of the high resistance of the single lumen within the double-lumen tube, and no changes in ventilation were made on the basis of increased airway pressure alone. Tube displacement or malposition was always excluded by fibre-optic inspection during any period of ventilatory difficulty.

Full monitoring was established, including invasive measurement of systemic blood pressure, central venous pressure, urine output, core temperature, and the usual airway and ventilation measurements. Measures were taken to maintain normothermia. Manipulation of the non-ventilated lung to maintain systemic oxygenation included insufflation of 100% oxygen (2–3 litre min^{-1}) and the application of 5–10 cm H_2O CPAP.

After surgery and before transfer to the intensive care unit, the patient was reintubated with an endonasal or endotracheal tube. Sedation was maintained with i.v. propofol and opiate. Early extubation was encouraged once the patient was regarded as cardiorespiratory-stable, normothermic and comfortable and if blood loss from the chest drains was less than 50 ml h^{-1}. When early extubation was not possible, the patient was ventilated overnight. After extubation, the patient remained in the intensive care unit until he or she could safely be transferred to a high dependency unit (HDU).

Post-operative analgesia was provided by a thoracic epidural infusion of 0.125% bupivacaine containing diamorphine 40 μg ml^{-1}, and adjusted in accordance with the patient's needs.

Area under the curve

To pharmacokineticists, the area under the concentration—time curve is an important measure of exposure to a drug or metabolite. When using estimates of exposure, determination of the area under the concentration–time curve (AUC) is customarily carried out using the trapezoidal method.[13] We used the analogy of hypotension or hypoxaemia as a metabolic toxin to which the patient was exposed to during the surgery. The measure of the exposure could then be determined by estimating the AUC.

Hypoxaemia index

Oxygen saturation recorded during OLV was plotted on a fixed linear scale of 0–100% against time for each patient and the AUC was calculated using the trapezoidal rule. The area was standardized for time by dividing the area by the OLV duration.

Hypotension index

A plot of mean arterial pressure (MAP) against time was made and the total AUC was calculated using a MAP of less than 70 mm Hg as the cut-off value. The hypotension index was then calculated by dividing the total AUC by the total duration of surgery.

Statistical analysis

Data were analysed using SPSS for Windows 8.1 (SPSS Inc., Chicago, IL, USA) under the Windows 95 operating system. Patients with data missing for a given variable were not included in univariant analysis for that variable. Initial univariant analysis, using the independent Student *t*-test for discrete variables and the χ^2 test for categorical variables, was used to compare patient outcomes (mortality, ARDS and respiratory failure) against individual pre-, peri- and post-operative variables. Multiple logistic regression analysis, using a forward conditional strategy, was then used to examine the importance and interaction of variables with respect to the outcome.

Results

ARDS occurred in 14.5% of all patients who underwent oesophagectomy for oesophageal cancer between January 1996 and December 1999. Intensive therapy unit (ITU) and hospital stays were prolonged in this group compared with patients who did not develop ARDS [mean (SD) ITU stay 16 (16) *vs* 1 (1) day; mean hospital stay 36 (34) *vs* 15 (8) days]. Mortality in the group with ARDS was 50% compared with 3.5% in the group without ARDS. ARDS-associated mortality accounted for 71% of total post-operative mortality. Post-operative respiratory failure occurred in 23.8% of all patients, and this group had a mean (SD) ITU stay of 17 (25) days. Mortality in this group was 37%. Specific respiratory complications occurred in 44% of all patients, including persistent pleural effusions (15%), prolonged pneumothoraces (4.1%) and hydropneumothoraces (1.8%), empyema (2.4%), chylothorax (2.4%), pneumonia (17.8%), pulmonary emboli (1.8%) and laryngeal oedema (*n*=1).

Variables associated with the development of ARDS are shown in Table 1. Pre-operative factors included a low pre-operative BMI and a history of cigarette smoking. Peri-operative instability was associated with ARDS, as indicated by the need for fluids and blood products during operation, the use of inotropes and peri-operative hypoxaemia and hypotension. Longer duration of procedure and length of time of OLV were also significant. Post-operatively, the need for emergency re-exploration for bleeding was associated with ARDS. The experience of the consultant surgeon, but not the consultant anaesthetist, was also associated with the development of ARDS (*P*=0.005). Risk factors for the development of acute lung injury and for overall mortality were identical to those for ARDS.

Multiple logistic regression analysis was used to determine the relative contributions of the variables to the development of ARDS (Table 2). In a forward conditional model, analysing the complete data on 146 patients, six factors were found to be significant. A low BMI and a past or current history of smoking were the only pre-operative factors of significance. Peri-operative instability, as indicated by hypoxaemia during OLV, hypotension and the need for fluids all increased the risk of post-operative ARDS. The factor with the highest odds ratio for the development of ARDS was the development of post-operative anastomotic breakdown.

Table 1 Results of univariable analysis of pre-, peri- and post-operative factors associated with the development of ARDS after oesophagectomy. Data are mean (SE) and 95% confidence interval (CI) or percentages. $P<0.05$ was considered significant

Variable	Number of patients	Mean (SE; CI) or percentage		*P*
		Non-ARDS group	ARDS group	
Current or ex-smoker	147	62%	92%	<0.004
BMI (kg m^{-2})	146	24.9 (0.4; 24.1–25.7)	21.8 (3.7; 14.5–29.1)	<0.002
OLV duration (min)	164	120 (3; 114–126)	136 (7; 122–150)	<0.02
Hypoxaemia index	164	3.3 (0.2; 2.9–3.7)	5.7 (0.7; 4.3–7.1)	<0.0001
Hypotension index	164	8.6 (0.8; 7.0–10.2)	17.4 (2.6; 12.3–22.5)	<0.0001
Ephedrine (mg)	164	4.0 (0.6; 2.8–5.2)	8.8 (1.8; 5.2–12.4)	<0.005
Inotrope infusion	164	0.7%	20.8%	<0.0001
Fluids infused (litres)	164	4.4 (0.1; 4.2–4.6)	5.0 (0.3; 4.4–5.6)	<0.027
Colloids (litres)	164	1.5 (0.1; 1.3–1.7)	2.0 (0.2; 1.6–2.4)	<0.002
Post-operative transfusions (units)	167	1.0 (0.2; 0.6–1.4)	5.3 (1.5; 2.3–8.3)	<0.0001
Total peri-operative transfusions (units)	167	1.6 (0.2; 1.2–2.0)	6.3 (1.6; 3.1–9.5)	<0.0001
Emergency re-exploration	168	4.9%	20.8%	<0.016
Post-operative leak	168	8.3%	41.6%	<0.0001

Table 2 Results of forward conditional multiple logistic regression analysis on 146 patients with complete data using factors found to be significant in the univariant analysis of ARDS. Data are given for each significant factor

Factor	Odds ratio	95% CI (lower)	95% CI (upper)	*P*
BMI	0.58	0.41	0.82	0.004
Smoker	9.95	1.07	92.7	0.04
Hypoxaemia index	1.76	1.26	2.47	0.001
Hypotension index	1.08	1.01	1.16	0.04
Fluids	2.98	1.16	7.67	0.04
Leak	22.52	3.16	160.36	0.002

Discussion

The recent Confidential Enquiry into Peri-Operative Deaths (CEPOP) recorded 'respiratory problems as being a major cause of morbidity and mortality after elective oesophageal surgery'.[1] This conclusion is supported by many published reports and a systematic review.[6] [14–19] The precise incidence of respiratory problems after oesophagectomy depends on definition, but Müller and colleagues, in their review,[19] reported the average incidence of postoesophagectomy respiratory failure to be 27% on the basis of a database of 83 783 patients drawn from 121 publications. The incidence of respiratory failure in our group (23.8%) was similar to that reported by Müller in his review series. Pulmonary complications occurred in 44% of our patients, and this group had prolonged hospital admissions and increased mortality.

ARDS is a major contributor to respiratory morbidity and mortality after oesophagectomy. In one series of 157 patients,[2] ARDS occurred in 17% of cases after a transthoracic approach and had a mortality of 78%. In a smaller series of 19 patients, ARDS was reported in 53%,[6] and in another report ARDS occurred in 33% of 18 patients.[18] The incidence of ARDS in our series was 14.5%, which is lower than in previous reports, although mortality in this group was high at 50%. In addition, patients with ARDS accounted for 71% of the total mortality after oesophagectomy.

ARDS is characterized clinically by impaired pulmonary gas exchange leading to hypoxaemia, and plain chest radiology showing diffuse alveolar infiltrates.[3] [20] Most patients will require some form of mechanical ventilatory support, often for a prolonged period. Despite modern intensive care, mortality remains high and most series report a survival rate of less than 50%.[4]

The precise cause of ARDS remains uncertain. It may represent a stereotyped response to a variety of direct and indirect insults to the lung. Most cases of ARDS are preceded by a major systemic insult between 24 and 48 h before the full clinical syndrome develops. Initial descriptions of the condition concentrated on pulmonary vascular permeability disturbances. More recent research has emphasized that ARDS is an inflammatory condition of the lung and that lung injury is probably initiated and perpetuated by a number of inflammatory mediators.[5] [21]

Rocker and colleagues[17] reported a high frequency of subclinical lung injury after oesophagectomy. They measured lung vascular permeability, using a double radioisotope technique, in nine consecutive patients. Although none developed clinical ARDS, all the patients showed an increase in lung permeability after operation. They also noted that lung permeability was higher on the thoracotomy side than on the dependent side after operation. Both local and systemic factors may therefore be important in the aetiology of postoesophagectomy ARDS.

Oesophagectomy involves a long period of OLV.[22] To optimize surgical access, the lung on the thoracotomy side is deliberately collapsed while the contralateral lung receives all the ventilation and most of the pulmonary blood flow. This procedure could result in lung injury to both the collapsed and dependent lung. There is much experimental data showing that even moderate mechanical ventilation may produce a form of micro-barotrauma indistinguishable from ARDS.[8] In addition, a recent large multicentre study of ARDS demonstrated more mortality in patients receiving conventional high tidal volume ventilation than those receiving lower tidal volume ventilation.[23] Relatively high tidal volumes are often used during OLV and could result in ventilator-induced lung injury.

Injury to the collapsed lung may follow lung reperfusion. Organ injury by reperfusion is well recognized, and there is good evidence for free radical-related lung injury in a number of experimental models of lung reperfusion injury.[7]

Systemic factors that may also result in lung injury include peri-operative endotoxaemia. One group has reported raised circulating endotoxin levels after oesophagectomy.[24] Endotoxin is a potent cause of lung injury in experimental animals, and ARDS commonly follows septic shock.[25] Major surgical injury, including oesophagectomy, also releases a number of proinflammatory cytokines, which may contribute to lung injury.[26]

A number of pre-operative factors have been linked to mortality after elective oesophagectomy, including age, lung function, arterial blood gases and the presence of chronic respiratory and liver disease.[14 16 27] Pre-operative screening procedures and case selection will affect the importance of these variables, as some centres may not operate on higher-risk patients. In our study, most pre-operative variables recorded were not associated with the development of post-operative complications. Only low BMI and a history of smoking were associated with ARDS, while peri-operative lung function and arterial blood gases did not predict the development of lung injury. The lack of association between these variables and outcome in our study could explain by our screening procedures and careful case selection.

There are few reports of the relationship between intraoperative variables and the post-operative course. One study of 269 patients found that intraoperative blood loss and the need for inotropic support were associated with post-operative mortality.[27] We are not aware of any previous study that has examined the relationship between cardiorespiratory instability during surgery and subsequent ARDS. Factors associated with ARDS include the durations of both surgery and OLV, surgical experience, the need for blood and fluid replacement during and after operation, the need for inotropic support during surgery, and cardiorespiratory instability, indicated by hypoxaemia and hypotension. The magnitude of the surgical stress and the patient's cardiorespiratory responses seem to be linked to the development of lung injury. These results support the hypothesis that tissue ischaemia/reperfusion injury contributes to ARDS.[7] Recurrent intraoperative episodes of hypoxaemia and hypotension cause a series of tissue ischaemia and reperfusion injuries, and thus the release of soluble, proinflammatory mediators, and activate circulatory leucocytes. Injury of the lungs and other distant organs is then the result of endothelial/epithelial cell damage caused by a soluble and cellular inflammatory response.

Our results are not unexpected in view of recent reports on the pre-operative optimization of high-risk patients.[9 10] In these studies, patients undergoing major elective surgery underwent invasive cardiac monitoring before surgery. Cardiac output was then augmented into the supranormal range using a combination of fluid and inotrope therapy. At least two randomized studies have reported significantly lower mortality in surgical patients receiving this therapy.[10]

Our finding could show the corollary of this approach. When no attempt is made to optimize cardiac output before operation, those patients who need more intraoperative fluid replacement and inotropes and have more hypotension and hypoxaemia have the worst outcome. This hypothesis is supported by a study of post-operative haemodynamics in 115 patients after oesophagectomy.[15] The patients who required prolonged ITU ventilation and those who died had worse post-operative haemodynamics than survivors.

In summary, we have found an association between various measures of intraoperative instability and the development of postoesophagectomy ARDS. These findings suggest the need for prospective studies to investigate the optimization of haemodynamics before and during major elective surgery. In addition, they suggest that the intraoperative cardiopulmonary management of high-risk surgical patients may have an important effect on outcome.

References

1 Sherry K. Management of patients undergoing oesophagectomy. In: Gray AJG, Hoile RW, Ingram GS, Sherry K, eds. *The Report of the National Confidential Enquiry into Peri-Operative Deaths 1996/1997*. London: National CEPOD, 1998; 57–61

2 Millikan KW, Silverstein J, Hart V, Blair K, Bines S, Roberts J, *et al.* A 15-year review of esophagectomy for carcinoma of the esophagus and cardia. *Arch Surg* 1995; **130**: 617–24

3 Wyncoll DLA, Evans TW. Acute respiratory distress syndrome. *Lancet* 1999; **354**: 497–501

4 Baudouin S. Improved survival in ARDS: chance, technology or experience? *Thorax* 1998; **53**: 237–8

5 Pittet JF, Mackersie RC, Martin TR, Matthay MA. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med* 1997; **155**: 1187–205

6 Katsuta T, Saito T, Shigemitsu Y, Kinoshita T, Shiraishi N, Kitano S. Relation between tumour necrosis factor alpha and interleukin 1beta producing capacity of peripheral monocytes and pulmonary complications following oesophagectomy. *Br J Surg* 1998; **85**: 548–53

7 Jordan MC, Mitchell JA, Quinlin GJ, Goldstraw P, Evans TW. The pathogenesis of lung injury following pulmonary resection. *Eur Respir J* 2000; **15**: 790–9

8 Dos Santos CC, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol* 2000; **89**: 1645–55

9 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *J Am Med Assoc* 1993; **270**: 2699–707

10 Boyd O, Street M. Is perioperative intensive care therapy useful in patients with limited cardiovascular reserve? *Curr Opin Crit Care* 1999; **5**: 393–9

11 Sutton DN, Wayman J, Griffin SM. Learning curve for oesophageal cancer surgery. *Br J Surg* 1998; **85**: 1399–402

12 Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al.* The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818–24

13 Gagnon RC, Peterson JJ. Estimation of confidence intervals for area under the curve from destructively obtained pharmacokinetic data. *J Pharmacokinet Biopharm* 1998; **26**: 87–102

14 Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. *Br J Surg* 1998; **85**: 840–4

15 Kusano C, Baba M, Takao S, Sane S, Shimada M, Shirao K, *et al.* Oxygen delivery as a factor in the development of fatal postoperative complications after oesophagectomy. *Br J Surg* 1997; **84**: 252–7

16 Nagawa H, Kobori O, Muto T. Prediction of pulmonary complications after transthoracic oesophagectomy. *Br J Surg* 1994; **81**: 860–2

17 Rocker GM, Wiseman MS, Pearson D, Shale DJ. Neutrophil degranulation and increased pulmonary capillary permeability following oesophagectomy: a model of early lung injury in man. *Br J Surg* 1988; **75**: 883–6

18 Schilling MK, Gassmann N, Sigurdsson GH, Regli B, Stoupis C, Furrer M, *et al.* Role of thromboxane and leukotriene B4 in patients with acute respiratory distress syndrome after oesophagectomy. *Br J Anaesth* 1998; **80**: 36–40

19 Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77**: 845–57

20 Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; 1334–49

21 Reid PT, Donnelly SC, Haslett C. Inflammatory predictors for the development of the adult respiratory distress syndrome. *Thorax* 1995; **50**: 1023–6

22 Tugrul M, Camci E, Karadeniz H, Senturk M, Pembeci K, Akpir K. Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia. *Br J Anaesth* 1997; **79**: 306–10

23 Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301–8

24 Moriyama H, Hirata S, Kubo Y. Alteration of serum levels of endotoxin, polymorphonuclear leukocyte elastase, and the molecular markers of the coagulation and fibrinolytic system in the patients with esophageal cancer and lung cancer before and following operation. *Rinsho Byori Jpn J Clin Pathol* 1995; **43**: 233–7

25 Ghosh S, Latimer RD, Gray BM, Harwood RJ, Oduro A. Endotoxin-induced organ injury. *Crit Care Med* 1993; **21**: S19–S24

26 Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery* 2000; **127**: 117–26

27 Ferguson MK, Martin TR, Reeder LB, Olak J. Mortality after esophagectomy: risk factor analysis. *W J Surg* 1997; **21**: 599–603

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Comparison of pattern of breathing with other measures of induction of anaesthesia, using propofol, methohexital, and sevoflurane[†]

T. L. Strickland and G. B. Drummond*

Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW, UK
**Corresponding author*

We assessed change of the pattern of breathing as a marker of induction of anaesthesia, using a method of maintaining spontaneous breathing throughout the induction period. We compared this index with a measure used clinically, the lash reflex, and measures used for drug investigations such as loss of grip of an object, cessation of finger tapping, and loss of arm tone. Ninety female patients (mean age 32 (17–63) yr, mean weight 63 (10) kg) were randomly allocated to induction of anaesthesia using propofol, methohexital, or sevoflurane. The i.v. agents were given by slow injection estimated to give an induction dose (for weight drop end point) in 90 s. Sevoflurane was given by progressively increasing the inhaled concentration to 8% so that induction should occur within 90–120 s. We measured time to change in breathing pattern, loss of voluntary finger tapping, loss of the lash reflex (tested at 15 s intervals), loss of postural tone in an outstretched arm, and loss of grip of a small metal cylinder held between finger and thumb. For methohexital and sevoflurane, the mean times for induction of anaesthesia occurred in the above order. With propofol, the lash reflex and tone were lost at the same time. The mean (SD) time to induction, by loss of arm tone was 64 (16) s for propofol, 83 (23) s for methohexital, and 94 (31) s for sevoflurane. The mean time to change in breathing pattern was 47 (20) s for propofol, 53 (14) s for methohexital, and 78 (29) s for sevoflurane. Although the time to achieve each end point was different, all the end points (except the lash reflex) appeared to provide similar measures of induction of anaesthesia. The pattern of breathing is an early sign of the onset of anaesthesia.

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Clinical investigations of induction of anaesthesia use a variety of measures of loss of consciousness. These include loss of verbal contact, loss of volitional activity such as finger tapping, loss of reflexes, and loss of muscle tone.[1–4] However, these tests may not be equivalent measures of anaesthesia. Dose–response curves for the separate tests may not be parallel for a given agent; for example the lash reflex may be lost before consciousness when propofol is used.[5] The dose–response curves may also vary depending on the induction agent used thus they may not be parallel for differing agents.[6]

Propofol and barbiturates are two commonly used anaesthetic induction agents; and for day case surgery, inhalation induction with sevoflurane is becoming more common.[7] However, some induction methods require considerable co-operation from the patient, such as vital capacity breaths or breath holding.[8] Asking the patient to hold their breath helps to prevent apnoea after induction of anaesthesia, but can upset the continued uptake of the anaesthetic. Respiration can also be better maintained if re-breathing is allowed to offset the effects of hypocapnia.[9 10] In our studies of this topic, we noted that breathing frequency and pattern changed noticeably and promptly to a different, regular pattern which could give an early and reliable index of loss of consciousness.

We designed the present study to compare the onset of regular breathing pattern with other frequently used end points of anaesthetic induction, both clinical and those used in investigations. We used three different induction agents—propofol, methohexitonal, and sevoflurane—which have possibly different patterns of action. We

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compared change in pattern of breathing with the more conventional estimates of induction of anaesthesia. We also considered the contention that conventional estimates of anaesthetic induction are not equivalent.

Methods

The study was approved by the local ethics committee. We studied patients about to have surgery in the gynaecology day case unit, and asked healthy, English speaking women, aged more than 16 yr, to give written, informed consent. Patients were not recruited if they had received any form of sedation or analgesia.

We used a blocked, randomized, parallel design. Patients were allocated in blocks of 30 to receive either propofol, methohexitonal, or sevoflurane as an induction agent by sealed envelopes. Three were withdrawn for technical reasons after allocation. These choices were replaced.

As the rate of administration of i.v. agents would affect the time taken to administer an induction dose, and the rate of administration affects the induction dose required, we attempted to give each patient the appropriate dose in the same time. We estimated the induction dose of thiopental, using the regression equation of Avram,[11] which takes age and weight into account:

Dose of thiopental (mg)=295+weight (kg)–age (yr)×1.86

The estimated induction dose (EID) of the i.v. agents was calculated using a relative potency for methohexital of 4.93[12] and 0.53 for propofol (personal data). This dose was increased by 50%, made up to 30 ml using 0.9% saline, and given from a Graseby 3500 syringe driver set to run at 800 ml h^{-1}, so that the EID would be given in about 90 s. The injection continued until all the end points had been reached or 150% of the EID had been given. The method of induction with sevoflurane did not require any change in the patient's breathing. We added sevoflurane 0.5% to the fresh gas. After three breaths, this was doubled to 1%. The concentration was doubled after each three breaths until the maximum concentration of 8% was reached. This level was then maintained until all the end points had been reached.

The patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Arterial pressure readings were not taken during induction of anaesthesia. Before induction started, the patient breathed from a coaxial Mapleson D circuit supplied with oxygen 3 litre min^{-1} and fitted with a pneumotachograph and a sidestream carbon dioxide analyser (Datex Cardiocap II). A good mask seal was obtained, checked by movement of the reservoir bag and a carbon dioxide trace that showed a satisfactory expiratory plateau and a secondary peak during inspiration, indicating re-breathing. The pressure from the pneumotachograph was measured with a transducer (Furness) and recorded with a digital logging device (Dash IV). A second channel recorded a signal voltage used to mark the end points of induction. The device also gave a paper printout of the two signals at 20 mm s^{-1}. After 45 s of regular breathing had been recorded, induction of anaesthesia was commenced.

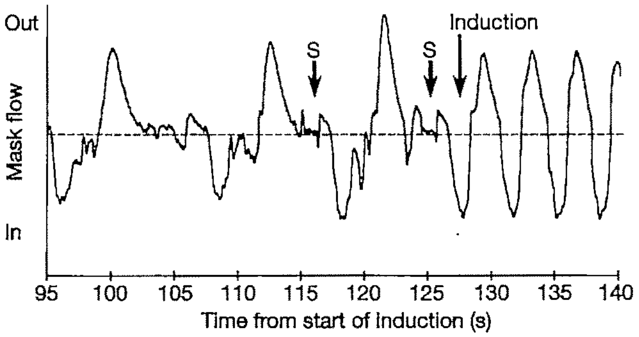

Fig 1 A good example of the change in respiratory pattern during induction of anaesthesia. Inspiratory flow is down. Swallowing during expiration (marked S) occurs in two breaths preceding the onset of a sudden change in frequency and pattern of flow.

Each patient lay supine on a horizontal table and a vein on the dorsum of the left hand was cannulated and connected to the infusion pump if appropriate. Before breathing from the mask was started, the right arm was held raised and straight, at 45% to the horizontal and away from the side of the body. The patient gripped a steel cylinder, 10 cm long, and 1.5 cm diameter, between the first finger and thumb of her right hand. She was asked to tap regularly with the index finger of the left hand, and to keep tapping, keep hold of the weight, and keep the arm up for as long as possible. The patient's lash reflex was tested every 15 s. The signal voltage to the recorder was switched to indicate the time the lash reflex vanished, when the patient finally stopped tapping her index finger, when her right arm came down to become horizontal, (loss of muscle tone) and when the weight was dropped. When all the end points were reached and a change in breathing pattern had been noted, or after the entire i.v. dose had been given, the recording was stopped and anaesthesia continued as indicated clinically. If the entire dose of methohexital or propofol was given without all the end points having occurred, only those end points that had been reached were analysed.

A separate printout was made of the respiratory flow record and coded to conceal the agent and patient from a single observer who measured the time that the pattern of respiration changed (Fig. 1). If there was no clear changeover in breathing pattern, the end of the last recognizable 'conscious' breath and the start of the first recognizable 'unconscious' breath were chosen and the midpoint calculated. We measured the time from start of induction to the time to achieve the other end points from the recording of the events.

Statistical analysis

The data were displayed visually as cumulative effect against administration time, and described using statistics

Table 1 Physical characteristics of the patients studied

		Age (yr)		Weight (kg)	
Agent	**Number**	**Mean**	**Range**	**Mean**	SD
Propofol	30	31	17–63	64	11
Methohexital	30	32	19–61	65	11
Sevoflurane	30	32	17–63	62	10

assuming a normal distribution. The coefficient of variation was taken as an index of the slope of the time–response curve. Responses were compared using ANOVA, and Minitab version 9. We compared the homogeneity of these coefficients with a method that allows comparisons of several variances.[13] Using a common coefficient of variation, derived from a weighted sum of the coefficients of variation in each group, the test generates a value similar to the chi-squared statistic for three or more groups. No statistical package was used for this calculation, but it was aided with Excel 2000. Significance was set at $P<0.05$.

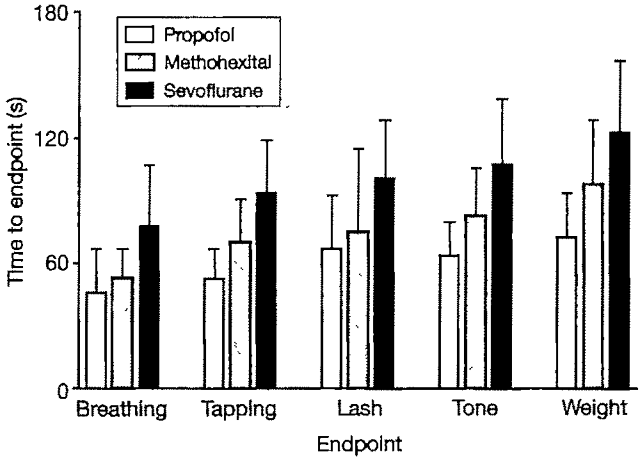

Fig 2 Mean time with SD to end point for the three agents. Propofol, open column; methohexital, shaded column; sevoflurane, filled column.

Results

We asked 132 patients to take part in the study, and 93 patients agreed to do so. Data from 30 patients in each group are presented: three patients were withdrawn for technical reasons. Patient details are given in Table 1. There were no serious complications during induction of anaesthesia and oxygen saturation remained above 95% in all patients.

The change in breathing pattern was easily determined as a single time in 22, 20, and 15 of the patients who received propofol, sevoflurane, and methohexital, respectively. A good example of the transition is shown in Figure 1. Breathing frequency always increased, and the flow pattern changed recognizably in all except one subject. However, the change was gradual in about one-third of the patients and the time of transition had to be determined by interpolation. Apnoea (absent respiratory flow for more than 10 s) occurred during induction of anaesthesia in 6, 3, and 2 of the patients receiving propofol, sevoflurane, and methohexital, respectively. These differences in incidence were not statistically different between the groups (Fisher's exact test). In all of these cases, the apnoea coincided with the change in pattern. The time of change could not be detected in one patient who received propofol.

One patient who received methohexital failed to drop the weight and this patient and five others (two propofol, three methohexital) still had a lash reflex after the entire i.v. dose had been given.

Propofol had a more rapid effect than the other agents. Apart from the lash reflex, the pattern of change in the end points was remarkably consistent (Figs. 2 and 3). Comparison of the agents using ANOVA showed that there were highly significant differences between the agents, using all the measures of induction. However, only with tapping, tone, and grip did the 95% CI for each distribution not overlap.

The effect of sevoflurane was delayed, presumably because of the progressive increase in the inhaled concentration, causing a delay before effective concentrations of the agent were being inhaled. The cumulative time curves appeared sigmoid (Fig. 3) and logit plots confirmed this. An example is shown in Figure 4.

The response that differed from the others was the lash reflex. The original data are shown as a solid line in Figure 3 and the corresponding logit plot in Figure 5. Compared with the logit for tone, where the slope is less for the slower acting agent (sevoflurane), the slopes for propofol and sevoflurane are parallel and the slope for the methohexitone response is less. To test this possibility, we compared the coefficient of variation of the responses. We chose this measure for comparison between the tests because the mean time to achieve the responses differed considerably, and as time progressed the variation increased (see Figs 2 and 3). The coefficients of variation are given in Table 2. The only end point with a difference in variance between the agents was the lash reflex ($P<0.01$). The best estimate of the coefficient, based on pooled data, is greatest for this response.

These observations are supported by sequence of loss of the responses in the individual subjects. The most likely sequence of response was breathing, tapping, tone, and grip; this sequence was found 53 times out of a possible 88. In contrast, the lash reflex was lost before arm tone in 9, 11, and 15 of the patients who received propofol, methohexital, and sevoflurane, respectively; that is only 35 times out of a potential 84.

For methohexital, but not for the other agents, there was a significant difference ($P<0.01$) in the coefficients of variance of each index. With this agent, the greatest coefficient of variation is for the lash reflex (Table 2).

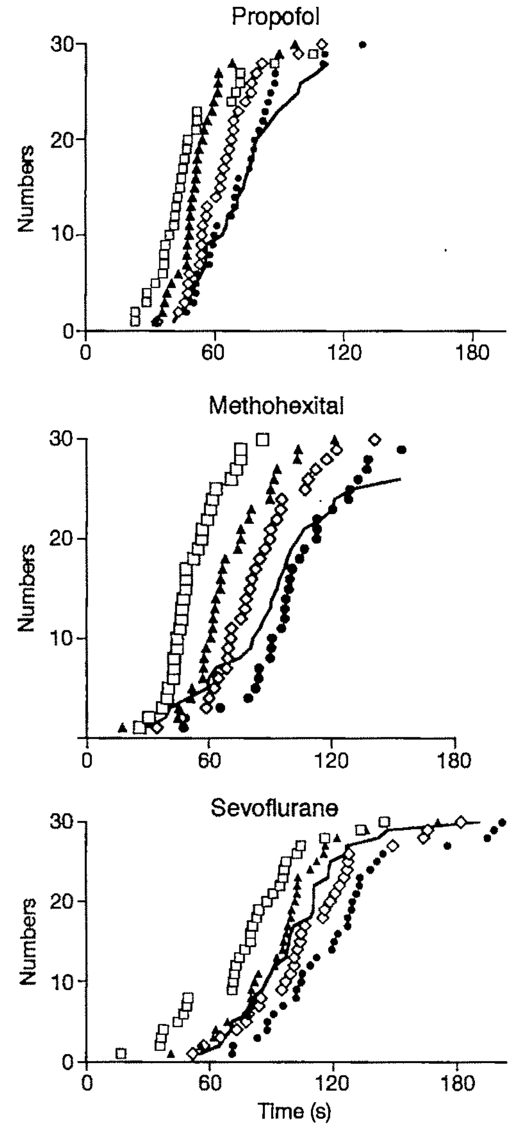

Fig 3 Cumulative response curves for the three agents. The responses shown in these panels are in sequence: open square symbols, breathing change; filled triangles, cessation of tapping; open diamonds, loss of arm tone; and filled circles, loss of grip. The loss of lash reflex overlaps some of these curves and is, therefore, shown as continuous lines. Six patients did not lose the lash reflex.

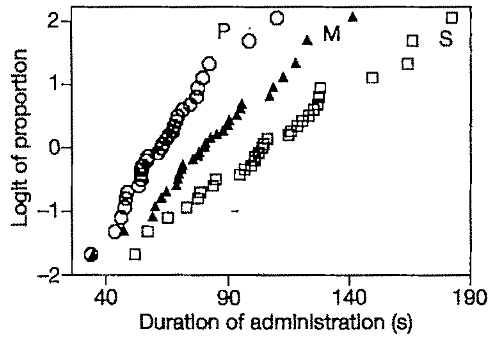

Fig 4 Cumulative response curves for the three agents, using a logit scale, for the loss of arm tone. Propofol, open circles; methohexital, closed triangles; and sevoflurane, open squares. The plots are straight, diverge, and do not overlap.

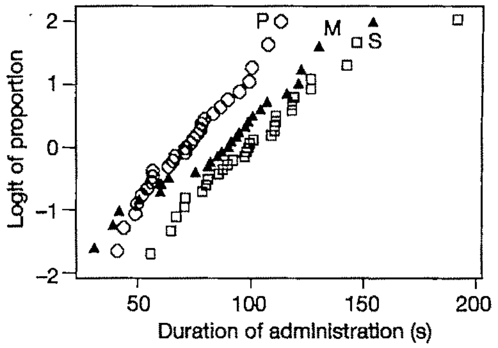

Fig 5 Cumulative response curves for the three agents, using a logit scale, for the loss of the lash reflex. Symbols as in Figure 4. The plots are straight, but do not diverge, and those for methohexital and propofol overlap.

Table 2 Comparison of coefficients of variation (%) for the tests, between agents and between drugs. Significant difference between agents, *$P<0.05$; and between tests, **$P<0.001$

Test	Propofol	Methohexital**	Sevoflurane	Best estimate
Tap	26	30	27	28
Tone	26	28	29	27
Weight	28	32	28	29
Lash*	39	54	28	40
Breathing	44	27	38	36

Discussion

We wished to relate the sign of automatic breathing to measures of induction, used in previous studies. Comparisons between studies are often impeded by the large variety of different measures used. These include loss of verbal contact,[14] closing the eyes,[15] loss of response to verbal command,[3 16 17] stopping a task such as finger tapping,[4] gripping a weight,[9 18 19 20] loss of a reflex such as the lash reflex,[21 22] or even combinations such as the lash reflex with finger tapping,[4 23] or verbal contact.[24 25] A recent large study of anaesthetic induction dose used a combination of verbal contact and response to physical contact.[26] Respiratory changes at induction of anaesthesia have not been studied, perhaps because the loss of the conscious component of the drive to breathe often causes apnoea at this time. Usually, use of breathing circuits has been directed towards avoiding re-breathing,[27] but hypocapnia is a frequent difficulty at induction.[9] Reliable inhalation induction without apnoea is possible if fresh gas flows are reduced,[10] and avoid the need to give patients instruction and practice.[8] Perhaps the mildly greater Pa_{CO_2} values in the subjects in this study may have altered the kinetic factors affecting anaesthetic action, but current evidence for a large effect is limited,[28] the pattern of responses is unlikely to be affected, and preliminary studies have not shown that mild re-breathing affects i.v.-induction (unpublished data).

For several reasons, we chose to compare times rather than doses in this study. First, the pattern of response loss was of more importance than the actual doses used. Second, one of the agents was inhaled, and estimating the 'dose' was not possible, particularly since as soon as the breathing pattern changed, the plateau pattern of exhaled gas composition was lost. However, it is likely that with induction occurring over this short period of time, the alveolar concentration of sevoflurane would still be increasing progressively.[8 29] Third, the kinetics of induction are far from simple[30] even though we chose drug infusion rates (typically about 160 mg kg^{-1} h^{-1}) that would have reduced the influence of administration rate on time to induction, and to a lesser extent the effect of administration rate on dose requirement.[26] The inter-relationship between kinetics and drug effect make acute studies, such as this one, uncertain grounds for speculation about drug effects. For example, propofol had a more rapid onset than we expected (i.e. appeared more potent), perhaps because the solution was diluted.[26]

Comparison of end points for a single drug are more valid, because the drug effect in this study will certainly have been progressively increasing. Previous studies have shown differences in slope of dose–response relationships for different end points, with the lash reflex generally having a greater variation in dose requirement.[5 20] We were surprised to find that breathing was such a sensitive indicator of anaesthetic effect. This suggests that the change in respiration is a sign of withdrawal of conscious control, which occurs before loss of other cortical control such as finger tapping. Another volitional act, handgrip, was extremely resistant to depression. Our impression was that this function appeared in our patients to have become a component of muscle tone. Our results are at variance with those of a study where propofol was slowly infused in volunteers, when a weight was dropped while the subject was awake, and before the lash reflex was lost.[20] Apart from the lash reflex, breathing change showed greater variation than the other tests, but this difference was not significant. A practical conclusion of this study is that breathing change is a sensitive index, but not very exact; and the most reliable and simple index is dropping of the outstretched arm, which is generally easily used clinically.

The response that is clearly different from the others is the lash reflex. Part of the greater variability of this measure might be caused by the intermittent measurements, but this could not explain the differences between agents. Anaesthesia is now not considered to be a single phenomenon.[31–33] In contrast to our other tests, which could be measures of a cortically mediated 'obtunding' effect, the lash reflex may indicate an 'immobilizing' effect that is less dependent on cortical effects,[34] although other studies have found a close relationship between lash reflex and response to verbal command[2] during propofol infusions. Further comparison between different agents with clinically relevant endpoints is justified.[35]

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References

1 Dunnet JM, Prys-Roberts C, Holland DE, Browne BL. Propofol infusion and the suppression of consciousness: dose requirements to induce loss of consciousness and to suppress response to noxious and non-noxious stimuli. *Br J Anaesth* 1994; **72**: 29–34

2 Forrest FC, Tooley MA, Saunders PR, Prys-Roberts C. Propofol infusion and the suppression of consciousness: the EEG and dose requirements. *Br J Anaesth* 1994; **72**: 35–41

3 Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. *Br J Anaesth* 1990; **65**: 346–52

4 Hall JE, Stewart JIM, Harmer M. Single-breath inhalation induction of sevoflurane anaesthesia with and without nitrous oxide: a feasibility study in adults and comparison with an intravenous bolus of propofol. *Anaesthesia* 1997; **52**: 410–5

5 Vuyk J, Engbers FHM, Lemmens HJM, *et al.* Pharmacodynamics of propofol in female patients. *Anesthesiology* 1992; **77**: 3–9

6 Prys-Roberts, C. A philosophy of anaesthesia: some definitions and a working hypothesis. In: Prys-Roberts C, Brown BR Jr, eds. *International Practice of Anaesthesia*. Oxford: Butterworth Heinemann 1996; vol 1,4: 1–14

7 Fredman B, Nathanson MH, Smith I. Sevoflurane for outpatient anesthesia: a comparison with propofol. *Anesth Analg* 1995; **81**: 823–8

8 Philip BK, Lombard LL, Roaf ER. Comparison of vital capacity induction with sevoflurane to intravenous induction with propofol for adult ambulatory anesthesia. *Anesth Analg* 1999; **89**: 623–7

9 Drummond GB, El-Farhan NMM. Do anxiety or hypocapnia predispose to apnoea after induction of anaesthesia? *Br J Anaesth* 1997; **78**: 153–6

10 Guracha Boru K, Drummond GB. Comparison of breathing methods for inhalation induction of anaesthesia. *Br J Anaesth* 1999; **83**: 650–3

11 Avram MJ, Sanghvi R, Henthorn TK, *et al.* Determinants of thiopental induction dose requirements. *Anesth Analg* 1993; **76**: 10–7

12 Berthoud MC, McLauglan GA, Broome IJ, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70**: 423–7

13 Zar JH. *Biostatistical Analysis*, 3rd edn. London: Prentice Hall International, 1996; 206–7

14 Peacock JE, Spiers SPW, McLauchlan GA, et *al.* Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients. *Br J Anaesth* 1992; **69**: 363–7

15 Baum VC, Yemen TA, Baum LD. Immediate 8% sevoflurane induction in children: a comparison with incremental sevoflurane and incremental halothane. *Anesth Analg* 1997; **85**: 313–6

16 Ruffle JM, Snider MT, Rosenberger JL, Latta WB. Rapid induction of halothane anesthesia in man. *Br J Anaesth* 1985; **57**: 607–11

17 Ruffle JM, Snider MT. Comparison of rapid and conventional inhalation inductions of halothane oxygen anaesthesia in healthy men and women. *Anesthesiology* 1987; **67**: 584–7

18 Crankshaw DP, Allt-Graham J. ED50 values for thiopentone, methohexital, propanidid and alfathesin: clinical experiment. *Anesth Intensive Care* 1978; **6**: 36–43

19 Cummings GC, Dixon J, Kay NH, *et al.* Dose requirements of ICI 35,868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–71

20 Leslie K, Sessler DI, Smith WD, *et al.* Prediction of movement during propofol nitrous oxide anesthesia – performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. *Anesthesiology* 1996; **84**: 52–63

21 Muzi M, Colinco MD, Robinson BJ, Ebert TJ. The effects of premedication on inhaled induction of anesthesia with sevoflurane. *Anesth Analg* 1997; **85**: 1143–8

22 Wilton NCT, Thomas VL. Single breath induction of anaesthesia, using a vital capacity breath of halothane, nitrous oxide and oxygen. *Anaesthesia* 1986; **41**: 472–6

23 Hall JE, Oldham TA, Stewart JIM, Harmer M. Comparison between halothane and sevoflurane for adult vital capacity induction. *Br J Anaesth* 1997; **79**: 285–8

24 Loper K, Reitan J, Bennett H, Benthuysen J, Snook L. Comparison of halothane and isoflurane for rapid anaesthetic induction. *Anesth Analg* 1987; **66**: 766–8

25 Naguib M, Sari-kouzel A, Seraj M, El-Gammal M, Gomma M. Induction dose-response studies with propofol and thiopentone. *Br J Anaesth* 1992; **68**: 308–10

26 Kazama T, Ikeda K, Morita K, *et al.* Investigation of effective anesthesia induction doses using a wide range of infusion rates with undiluted and diluted propofol. *Anesthesiology* 2000; **92**: 1017–28

27 Conway CM, Seeley HF, Barnes PK. Spontaneous ventilation with the Bain anaesthetic system. *Br J Anaesth* 1977; **49**: 1245–9

28 Brian JE. Carbon dioxide and the cerebral circulation. *Anesthesiology* 1998; **88**: 1365–86

29 Yasuda N, Lockhart SH, Eger EI, *et al.* Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991; **72**: 316–24

30 Krejcie TC, Avram MJ. What determines anesthetic induction dose? It's the front-end kinetics, doctor! *Anesth Analg* 1999; **89**: 541–4

31 Kissin I. General anesthetic action: an obsolete notion? *Anesth Analg* 1993; **76**: 215–8

32 Prys-Roberts C. Anaesthesia: a practical or impractical construct? *Br J Anaesth* 1987; **59**: 1341–5

33 Eger EI, Koblin DD, Harris RA, *et al.* Hyopthesis: inhaled anesthetics produce immobility and amnesia by different mechanisms at different sites. *Anesth Analg* 1997; **84**: 915–21

34 Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; **78**: 707–12

35 Dwyer R, Bennett HL, Eger EI, Heilbron D. Effects of isoflurane and nitrous-oxide in subanesthetic concentrations on memory and responsiveness in volunteers. *Anesthesiology* 1992; **77**: 888–98

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Uptake of isoflurane during prolonged clinical anaesthesia

S. K. Pal[1]*, G. G. Lockwood[2] and D. C. White[3]

[1]St Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital, Chelmsford, Essex CM1 7ET, UK. [2]Department of Anaesthesia, Imperial College School of Medicine, London, UK. [3]Department of Anaesthesia, Northwick Park Hospital, London, UK

**Corresponding author*

Recent evidence has suggested that the rate of uptake of inhalational anaesthetic is constant during maintenance of anaesthesia, contrary to the predictions of multi-compartment uptake models. We measured isoflurane uptake using a totally closed anaesthetic system during up to 10 h of stable anaesthesia for maxillo-facial surgery on 12 adult patients. Liquid isoflurane was injected into the system under computer control to produce an end tidal concentration of 1.3 MAC of isoflurane. Bench tests demonstrated that the leakage from the system was less than 8 μl min^{-1}, confirming that the rate of injection of isoflurane into the system was a close upper bound on the patients' uptake. Anaesthetic usage for a 70 kg patient was $0.44e^{-0.51t}+0.044e^{-0.013t}+0.058e^{-0.00098t}$ ml min^{-1} of liquid isoflurane, where *t* is duration of anaesthesia in minutes. There was a continuing reduction in anaesthetic requirement even at the end of the period of study that was statistically significant. These data do not support the notion that isoflurane uptake is constant during stable maintenance of anaesthesia but is compatible with the conventional multi-compartment model of anaesthetic uptake and distribution.

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The uptake of inhalational anaesthetic agents by the body is a subject of both practical and theoretical interest. During induction, an anaesthetizing partial pressure is achieved rapidly at the well-perfused site of action in the brain, but to maintain this partial pressure, anaesthetic must be continuously supplied to meet uptake elsewhere in the body. The total load of anaesthetic is a major factor determining the amount of metabolism and the formation of possibly toxic metabolites. The multi-compartment model of anaesthetic uptake and distribution has been promulgated for many years[1 2] and has much experimental evidence to support it.[2–7] The model represents the human body by a few compartments, each of homogeneous composition and perfusion. Anaesthetic is assumed to accumulate in each compartment at a rate proportional to its perfusion, the partial pressure difference between arterial blood and the compartment, and the solubility of the gas in that compartment. Measurements of the graded manner in which uptake proceeds (i.e. the shape of the uptake curve), provide evidence of the physical factors responsible for the distribution of anaesthetic in the body.

The multi-compartment model has never been accepted universally,[8] and recent work has been interpreted as evidence that anaesthetic uptake is constant after the first few minutes of inhalational anaesthesia.[9] We have investigated this controversy by measuring the uptake of isoflurane during prolonged anaesthesia. We studied 20 patients undergoing reconstructive head and neck surgery using a computer-controlled closed anaesthetic breathing system into which isoflurane was injected to maintain a concentration of 1.3 MAC.

Methods

The breathing system

The apparatus used was a functionally closed breathing system, delivering oxygen automatically via a 'gas piston'.[10 11] Mechanical ventilation is transmitted from the Y-connector of an Ohmeda 7900 ventilator (Ohmeda, Madison, USA) to the breathing system by a volume of gas acting as a piston in a 6 m 'trunk' of 22 mm corrugated plastic tube. There is no conventional fresh gas supply to this system, but some of the oxygen oscillating in the trunk is retained in the circle as oxygen there is consumed by the patient.[12] Liquid isoflurane is injected directly from a glass

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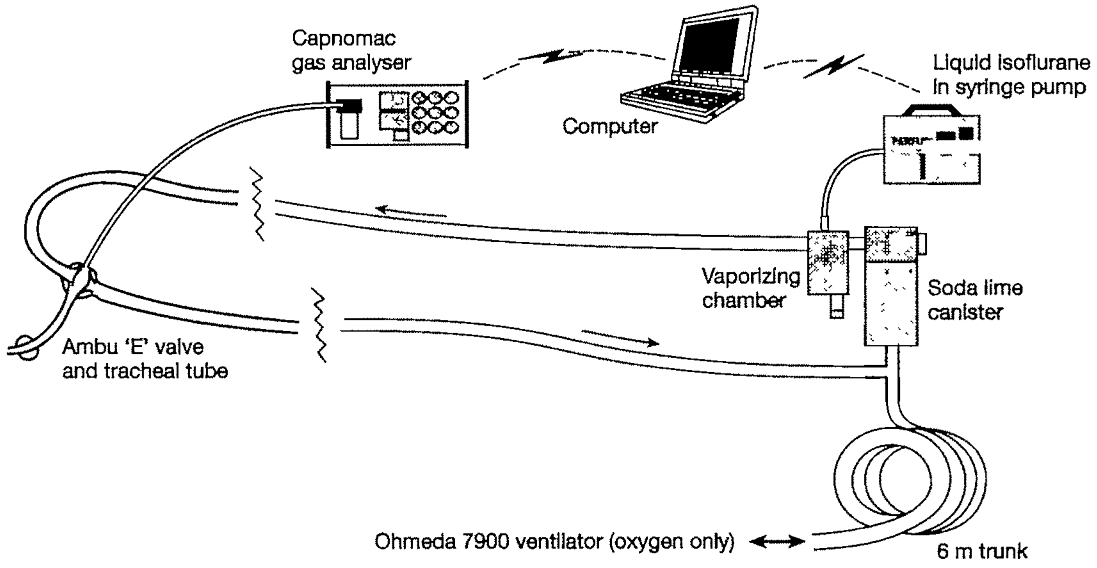
Capnomac gas analyser
Computer
Liquid isoflurane in syringe pump
Vaporizing chamber
Soda lime canister
Ambu 'E' valve and tracheal tube
Ohmeda 7900 ventilator (oxygen only)
6 m trunk

Fig 1 The breathing system. There is no conventional fresh gas flow oxygen being drawn up the trunk to replace volume lost from the breathing system from oxygen consumption. The anaesthetist sets the target end-expired isoflurane concentration on the computer, which then controls the rate of the syringe pump to achieve and maintain that value on the basis of measurements made by the gas analyser.

syringe (GT-50, SGE Europe Ltd, Milton Keynes, UK) into an in-circle vaporizing chamber (Fig. 1). The concentration of isoflurane within the system is measured by a Capnomac (Datex, Helsinki) multi-gas analyser, which was calibrated before use. The sampled gas is returned to the breathing system. A computer communicates with both this analyser and the isoflurane syringe pump, and controls the rate of isoflurane injection to achieve and maintain a predetermined end-expired concentration.

Bench test

Anaesthetic loss from the breathing system was measured using a model lung.[13] The model lung consisted of a 22.2 litre glass bottle with a tracheal tube inserted through its stopper. To prevent any absorption of volatile anaesthetics, the internal surface of the bung was covered with aluminum foil and the exterior of the assembly was covered with a silicone sealant. The model lung was attached to the breathing system in place of a patient. The system was ventilated with a tidal volume of 650 ml at a rate of 10 min^{-1}, producing a peak pressure of 25 cm H_2O. Isoflurane was injected into the vaporizing chamber as described above, until its concentration in the circuit reached 3%. The injection pump was then stopped and an estimate of the rate of anaesthetic loss from the system was calculated from the wash-out curve.[13] This is the obligatory loss, and is less than we expect to occur clinically.

Conduct of anaesthesia

After Ethics Committee approval and informed consent had been obtained, 20 patients undergoing head and neck surgery, were studied. A multi-disciplinary team of maxillofacial, ENT, and plastic surgeons were involved to undertake these lengthy surgical procedures, some of which lasted up to 18 h. The surgery involved excision of tumour and reconstruction of the defect with a free tissue flap. The patients received oral temazepam premedication. Anaesthesia was induced with propofol 2.5 mg kg^{-1} and fentanyl 4 μg kg^{-1}. A laryngeal mask airway (LMA[†]) was then inserted, the patients were connected to a closed breathing system, and controlled ventilation was instituted. Liquid isoflurane was injected as described above to achieve and maintain an end-expired concentration of 1.5%. The airway was then secured by percutaneous dilatational tracheostomy. Atracurium (0.5 mg kg^{-1}) was used to facilitate insertion of the tracheostomy tube; no further dose of muscle relaxant was administered. The closed breathing system was then disconnected from the laryngeal mask and connected to the cuffed tracheostomy tube. Anaesthesia was continued with 1.5% end-expired isoflurane and an infusion of fentanyl at 0–5 μg kg^{-1} h^{-1}. The end-expired carbon dioxide was maintained at 4.5 kPa.

Arterial and central venous catheters were placed using the radial artery and femoral vein respectively. ECG, arterial blood pressure, urine output, temperature (core and peripheral), haemoglobin and haematocrit, arterial blood acid–base status, fluid intake, and blood loss were monitored throughout. Temperature was maintained by surface warming (Bair Hugger, Eden Prairie, MN, USA). During the first 30 min of anaesthesia, it was occasionally necessary to treat hypotensive episodes with a 3-mg bolus of ephedrine. Thereafter, satisfactory blood pressure was maintained by infusion of i.v. fluid at 6–8 ml kg^{-1} h^{-1}, using Hartmann's solution and Gelofusine (Braun,

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[†] LMA® is the property of Intavent Limited.

Melsungen, Germany) in a ratio of 4:1. Blood was given as required to maintain the haemoglobin concentration between 8 and 10 g dl^{-1}. In closed systems the inspired oxygen fraction ($F\text{I}_{\text{O}_2}$) reduces as nitrogen accumulates as a result of: (i) wash-out from the patient[14] and (ii) the addition of air from the Capnomac oxygen reference flow, which is added to the sample return flow at a rate of 24 ml min^{-1}. $F\text{I}_{\text{O}_2}$ was maintained above 0.3 by intermittently venting the sample returned from the Capnomac so that oxygen entered the system from the gas piston. Any leak in the system revealed itself by an increase in $F\text{I}_{\text{O}_2}$ as oxygen from the gas piston replaced volume lost from the system.

Data analysis

The recorded rate of injection was normalized to 70 kg in proportion to each patient's body weight. The patient results were too noisy to allow useful individual analysis. The parameters of the function $\Sigma A_i e^{-k_i t}$ were adjusted to produce the best (i.e. least squares) simultaneous fit to the data, using an iterative technique on a spreadsheet (Solver, Microsoft Excel 97 SR-1). This function is the mathematical representation of exponential wash-in to multiple compartments. The significance of improvement in curve fit with increasing numbers of compartments was assessed using an F-ratio test.[15] If these pharmacokinetic compartments are associated with the classical vessel rich, muscle and fat tissue groups, then compartment volumes and perfusions can be calculated. The amount of isoflurane in each compartment is given by integrating the appropriate term in the equation from zero to infinity. At 37°C the vapour volume of isoflurane is 207 times the liquid volume, and remembering that the equilibrium tissue concentration of isoflurane is $1.5\lambda_{TG}\%$, where λ_{TG} is the tissue:gas partition coefficient, we deduce that the volume of the ith compartment is $207\,A_i/(0.015 \cdot k_i \cdot \lambda_{TG})$ ml. The compartment perfusion is derived from the rate constant: $k_i = q\lambda_{BG}/\lambda_{TG}$, where λ_{BG} is the blood:gas partition coefficient for isoflurane and q is the perfusion in units of ml blood (ml tissue)$^{-1}$ min^{-1} (see Table 2 for the values of partition coefficient used).

Simple linear regression was used to test the hypothesis that the rate of isoflurane uptake was continuing to reduce during the terminal period of our study (400–600 min).

Results

Patient characteristics are given in Table 1. The conduct of anaesthesia was satisfactory in all cases. Temperature was maintained at 37°C (core) and >35°C (peripheral). Urine output was between 2 and 2.5 ml kg^{-1} h^{-1}. Blood loss was in the range of 1500–2000 ml. Three bench tests were carried out to measure leakage from the system using the artificial lung and leakage was found to be 3, 7, and 8 µl min^{-1} of liquid isoflurane.

The records of six patients were discarded from the series because a failure of nitrogen accumulation indicated excessive leak from the system, most probably from the tracheostomy site. Records from two other patients were rejected because the target concentration was changed during the anaesthetic. A full set of the data can be obtained from http.//bja.oupjournals.org. The mean rate of decrease of oxygen concentration among the patients whose results are included in the analysis was 0.12% min^{-1} (minimum 0.05% min^{-1}). There was a clear correlation of isoflurane requirement with patient weight: at 3 h the cumulative uptake correlated significantly with weight (n=11, r^2=0.76, P<0.0005). Figure 2 shows the rate of isoflurane injection, normalized for each patient by simple proportion to 70 kg, together with the number of patients contributing data at those times. The data were compatible with a three-compartment model. The line of best fit is shown in bold in Figure 2 and is given by $0.44e^{-0.51t}+0.044e^{-0.013t}+0.058e^{-0.00098t}$ ml min^{-1} of liquid isoflurane for a 70 kg patient, where t is the duration of inhalational anaesthesia in min. The slope of the regression line through the last 200 min of weight-corrected data was significantly different from zero (95% CI from –0.000075 to –0.000055 ml min^{-2} liquid isoflurane). The regression line through individual data was also significantly less than zero (P<0.005) for all but one patient—the soda lime was changed at 520 min in that case, distorting the data.

Table 1 Patient characteristics. Duration refers to duration of data collection; terms in parentheses indicate that data collection had terminated before the end of the time period

Age (yr)	**Weight (kg)**	**Duration (min)**	**Cumulative uptake (ml liquid isoflurane)**	
			at 3 h	**at 10 h**
45	70	298	16.0	(22.6)
36	118	>600	25.7	53.4
45	69	>600	16.8	36.2
25	80	288	16.2	(22.4)
49	70	159	(13.3)	(13.3)
42	60	>600	8.7	20.2
50	69	>600	12.1	26.2
73	58	>600	7.8	20.0
49	60	594	10.8	(24.0)
69	65	543	10.8	(23.7)
38	68	513	14.6	(30.9)
44	86	290	13.6	(20.3)

When a value of 8 µl min^{-1} or less was subtracted from every usage datum point to give an estimate of uptake, the changes were modest: $0.44e^{-0.51t}+0.043e^{-0.013t}+0.051e^{-0.0012t}$ ml min^{-1} of liquid isoflurane for a 70 kg patient. The characteristics of the derived compartments are listed in Table 2.

Discussion

We have measured the rate of anaesthetic usage and, because the system is closed, we use it as an estimate of the rate of anaesthetic uptake. Our bench tests have shown a loss of up to 8 µl min^{-1} from a sealed model lung and we expect that leak around the airway will result in greater

Table 2 Compartmental data derived from modelling, assuming the compartment solubilities shown in the first line and a blood:gas partition coefficient of 1.4. The rightmost columns show the cardiac output implied by the results. (Abbreviations: VRG, vessel rich group; $\lambda_{T:G}$, isoflurane tissue:gas partition coefficient; C.O., cardiac output derived by summing compartmental blood flows)

Data	**VRG ($\lambda_{T:G}$ 2.5)**		**Muscle group ($\lambda_{T:G}$ 2.1)**		**Fat ($\lambda_{T:G}$ 70.5)**		**C.O. (litres min^{-1})**
	Volume (litres)	**Perfusion (ml 100 ml^{-1} min^{-1})**	**Volume (litres)**	**Perfusion (ml 100 ml^{-1} min^{-1})**	**Volume (litres)**	**Perfusion (ml 100ml-1 min-1)**	
Usage	4.8	91	23	1.9	12	4.9	5.3
Uptake	4.8	91	22	1.9	8.2	6.2	5.2

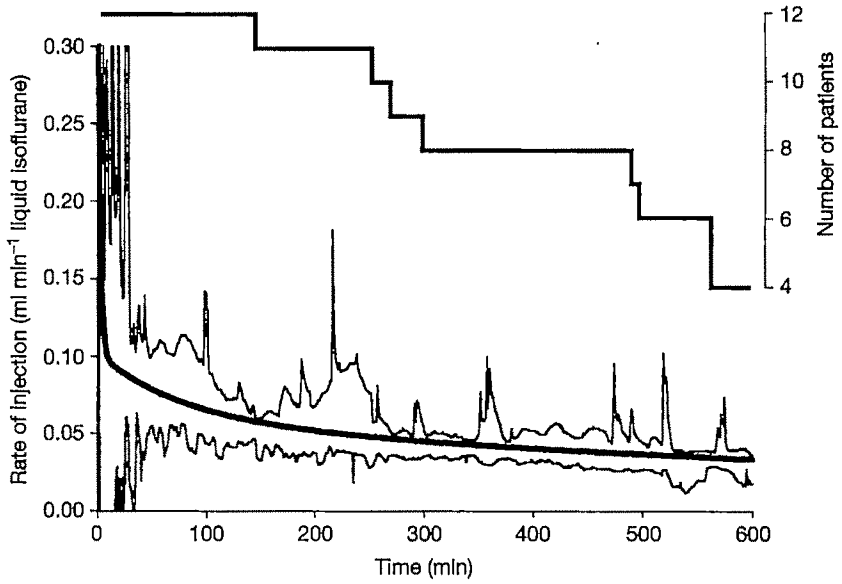

Fig 2 Left hand scale. Irregular lines: 5th and 95th percentiles of liquid isoflurane required to maintain an end-expired concentration of 1.5%, normalized for each patient to 70 kg. Bold, smooth line: curve of best fit. Right hand scale: number of patients contributing data at each time point.

losses in clinical use. There are additional leaks when the airway is manipulated early in the procedure, when the system is flushed and during changes of soda lime. We have found no formal data-processing algorithm that allows for these and have rejected the alternative approach of manual adjustment of the data until it 'looks right'. We prefer instead to use our data to indicate what must be the upper bounds on actual uptake. The additional losses tend to mask a gradual reduction in anaesthetic requirement. We have been able to demonstrate that a gradual decrease in uptake occurs. Our results are important because of the long duration of the measurements and the fact that we have been generous in the inclusion of losses that work against our significant result. Because these data can be analysed using a variety of methods we have provided access to our original data, so that other workers may inspect or use them.

Uptake by the patient does not necessarily imply accumulation within the body. Losses of anaesthetic by diffusion through skin,[16] mucous membrane, from wounds,[17] urine, and metabolism[18] should be insignificant. Assuming the solubilities of isoflurane in urine and saline are the same, the loss is approximately 9 ml of isoflurane vapour per litre of urine, or 0.5 μl min^{-1} liquid isoflurane for our patients. The isoflurane content of the blood loss would have been an order of magnitude less. We are aware of only one mechanism by which our results could underestimate uptake. Methane can accumulate in closed breathing systems and has been reported to cause a gas analyser such as ours to read 0.79% halothane spuriously during total i.v. anaesthesia.[19] The gain used in the infra-red system is less when isoflurane is selected and so methane would cause a lesser reading of 0.13% with isoflurane.[20] That could mean that we were maintaining only 1.37% isoflurane (the remainder of the 1.5% being a spurious contribution from methane), resulting in a 9% underestimate of anaesthetic uptake at a true 1.5% concentration.

Airway manipulation and temporary disconnections of the breathing system resulted in very noisy data sets, especially during the first 30 min of anaesthesia. It is surprising that the mean uptake figures during this period have such plausible values. These noisy data detract less from the accuracy of our uptake measurements later in the anaesthetic, which was the main focus of this study.

Our results show that anaesthetic uptake continues to reduce for 10 h. That may seem to run counter to a recent statement by Hendrickx and co-workers that uptake becomes effectively constant after a 4 min wash-in period.[9] Lin too has claimed that uptake is constant.[8] There are three reasons that make this contradiction more apparent than real. First, we agree with the editorial[21] accompanying Hendrickx's work that his results show uptake reducing throughout the first 49 min, not constant from 4 min. Second, we have presented our results in terms of rate of uptake, not cumulative uptake. The small, continued reduction in rate of uptake would indeed become almost negligible when viewed atop the accumulated load of isoflurane. Finally, we have been careful to keep our breathing system as near completely closed as possible. A small but constant leak, as might occur in routine use, would require an increase in anaesthetic delivery to counter it, so the reduction in anaesthetic uptake would be a smaller part of the rate of anaesthetic use and therefore less easy to discern. Thus, although we can agree that, for *clinical* purposes, isoflurane uptake becomes almost constant after a period of wash-in, uptake actually continues to reduce over a period of at least 10 h. Our results are compatible with the conventional perfusion-limited model of anaesthetic uptake and distribution.

References

1 Papper EM, Kitz RJ. *Uptake and Distribution of Anesthetic Agents.* New York: McGraw-Hill, 1963

2 Eger EI, 2nd. *Anesthetic Uptake and Action.* Baltimore: Williams and Wilkins, 1974

3 Mapleson WW. The rate of uptake of halothane vapour in man. *Br J Anaesth* 1962; **34**: 11–18

4 O'Callaghan AC, Hawes DW, Ross JAS, White DC, Wloch RT. Uptake of isoflurane during clinical anaesthesia. *Br J Anaesth* 1983; **55**: 1061–4

5 Carpenter RL, Eger EI, 2nd, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. *Anesth Analg* 1986; **65**: 575–82

6 Yasuda N, Lockhart SH, Eger EI, 2nd, et *al.* Kinetics of desflurane, isoflurane, and halothane in humans. *Anesthesiology* 1991; **74**: 489–98

7 Yasuda N, Lockhart SH, Eger EI, 2nd, *et al.* Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991; **72**: 316–24

8 Lin CY. Uptake of anaesthetic gases and vapours. *Anaesth Intens Care* 1994; **22**: 363–73

9 Hendrickx JFA, Soetens M, van der Donck A, Meeuwis H, Smolders F, de Wolf A. Uptake of desflurane and isoflurane during closed circuit anesthesia with spontaneous and controlled mechanical ventilation. *Anesth Analg* 1997; **84**: 413–8

10 Lockwood GG, Chakrabarti MK, Whitwam JG. A computer controlled anaesthetic breathing system. *Anaesthesia* 1993; **48**: 690–3

11 Devchand D, Chakrabarti MK, Lockwood GG. The uptake of enflurane during anaesthesia. *Anaesthesia* 1995; **50**: 491–5

12 Jordan M, Bushman JA. Closed-circuit halothane and enflurane using an in-circle Goldman vaporizer. *Br J Anaesth* 1981; **53**: 1285–90

13 Lockwood GG, Chakrabarti MK, Whitwam JG. An evaluation of anaesthetic loss from a closed breathing system. *Anaesthesia* 1993; **48**: 564–7

14 Barton N, Nunn JF. Totally closed circuit nitrous oxide/oxygen anaesthesia. *Br J Anaesth* 1975; **47**: 350–7

15 Boxenbaum HG, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. *J Pharmacokinet Biopharm* 1974; **2**: 123–48

16 Fassoulaki A, Lockhart SH, Freire BA, et *al.* Percutaneous loss of desflurane, isoflurane, and halothane in humans. *Anesthesiology* 1991; **74**: 479–83

17 Laster MJ, Taheri S, Eger EI, Liu J, Rampil IJ, Dwyer R. Visceral losses of desflurane, isoflurane, and halothane in swine. *Anesth Analg* 1991; **73**: 209–12

18 Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. *Anesthesiology* 1975; **43**: 325–32

19 Versichelen L, Rolly G, Vermeulen H. Accumulation of foreign gases during closed-system anaesthesia. *Br J Anaesth* 1996; **76**: 668–72

20 Guyton DC, Gravenstein N. Infrared analysis of volatile anesthetics: impact of monitor agent setting, volatile mixtures, and alcohol. *J Clin Monit* 1990; **6**: 203–206

21 Eger EI. Complexities overlooked: things may not be what they seem. *Anesth Analg* 1997; **84**: 239–40

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Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit

R. M. Venn[1]*, A. Bryant[2], G. M. Hall[2] and R. M. Grounds[3]

[1]*Department of Anaesthesia and Intensive Care, Worthing Hospital, Lyndhurst Road, Worthing, West Sussex BN11 2DH, UK.* [2]*Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK.* [3]*Department of Anaesthesia and Intensive Care Medicine, St George's Hospital, Blackshaw Road, London SW17 0QT, UK*

**Corresponding author*

We have compared the effects of dexmedetomidine and propofol on endocrine, metabolic, inflammatory and cardiovascular responses in patients in the intensive care unit (ICU) after major surgery. Twenty patients who were expected to require 8 h of post-operative sedation and ventilation were allocated randomly to receive either an infusion of dexmedetomidine 0.2–2.5 $\mu g\ kg^{-1}\ h^{-1}$ or propofol 1–3 $mg\ kg^{-1}\ h^{-1}$. Arterial pressure, heart rate and sequential concentrations of circulating cortisol, adrenocorticotrophic hormone (ACTH), growth hormone, prolactin, insulin, glucose and interleukin 6 were measured. An ACTH stimulation test was performed in all patients who received dexmedetomidine. Heart rate was significantly lower in the dexmedetomidine patients. There were no differences in arterial pressure, cortisol, ACTH, prolactin and glucose concentrations between the two groups. A positive response to the ACTH stimulation test varied depending on the diagnostic criteria used. The insulin concentration was significantly lower in the dexmedetomidine group at 2 h (P=0.021), although this did not affect blood glucose concentrations. Growth hormone concentrations were significantly higher in dexmedetomidine-treated patients overall (P=0.036), but circulating concentrations remained in the physiological range. Interleukin 6 decreased in the dexmedetomidine group. We conclude that dexmedetomidine infusion does not inhibit adrenal steroidogenesis when used for short-term sedation after surgery.

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The majority of patients admitted for ventilation to the intensive care unit (ICU) after surgery require sedation and analgesia to reduce anxiety, tolerate mechanical ventilation and provide pain relief. Inappropriate sedation techniques can, however, cause morbidity and even mortality in the ICU, as occurred with the use of long-term infusions of the imidazole agent etomidate.[1] Etomidate suppresses adrenocortical function by dose-dependent, reversible inhibition of two mitochondrial cytochrome P450 enzymes (P450c11 and P450scc), and this effect may persist for 24 h in critically ill patients after a single dose of etomidate.[2]

The highly selective and potent α_2 agonist dexmedetomidine is an effective agent for post-operative sedation and analgesia in the ICU.[3] It is an imidazole compound and therefore has the potential to exert similar inhibitory effects to etomidate on cortisol synthesis. *In vitro* and *in vivo* animal studies have shown that dexmedetomidine inhibits cortisol synthesis at concentrations above 10^{-6} M, whereas therapeutic plasma concentrations of dexmedetomidine in patients are less than 10^{-9} M.[4] Consequently, inhibition of steroidogenesis is unlikely to occur clinically, and this supposition is supported by the absence of hypocortisolism in human volunteers and surgical patients after i.v. or i.m. use.[5 6] However, inhibition may become important clinically when dexmedetomidine is given as an infusion in the ICU patient, especially if changes in circulating inflammatory mediators [tumour necrosis factor α, immunoreactive corticostatin, interleukin 6 (IL-6)] have already impaired the adrenocortical response to adrenocorticotrophic hormone (ACTH).[7]

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Attenuation of the cardiovascular and neuroendocrine responses to surgery may improve outcome by beneficial effects on organ function,[8] although modulating the inflammatory response is probably more important in improving recovery.[9] The modification of cardiovascular responses after surgery by dexmedetomidine has been described recently.[3] The neuroendocrine effects of the α_2-adrenoceptor agonist clonidine are well known[10 11] but have not been observed during surgery.[12 13] However, dexmedetomidine modified the pituitary hormonal response to gynaecological laparoscopy,[6] possibly because of its higher selectivity for the α_2-adrenoceptor. There has been little work on the effect of α_2-adrenoceptor agonists on the inflammatory response. Although IL-6 production is suppressed *in vitro* by *p*-aminoclonidine,[14] oral premedication with clonidine had no effect on the IL-6 response after pancreatobiliary surgery.[15]

We compared the effects of dexmedetomidine and propofol on adrenocortical function and the cardiovascular, endocrine and inflammatory responses in post-operative patients requiring sedation and ventilation in the ICU.

Methods

The local research ethics committee of St. George's Healthcare approved the study (reference number 98.06.8) and written informed consent was obtained from all patients. We studied 20 adult patients (age 18 yr or older) admitted to the ICU after complex major abdominal or pelvic surgery and who were expected to require 8 h post-operative sedation and ventilation. Exclusion criteria were allergy to any of the trial drugs, pregnancy, severe hepatic disease, requirement for haemodialysis or haemofiltration, spinal or epidural anaesthesia, use of etomidate in the preceding 24 h or a history of corticosteroid treatment within the last 3 months.

The anaesthetic technique was decided by the individual anaesthetist and the dose of intra-operative analgesic was recorded. On arrival in the ICU, patients were allocated randomly, using sealed envelopes, to receive either dexmedetomidine or propofol infusions together with an alfentanil infusion for analgesia if required. Patients received a loading dose of dexmedetomidine 2.5 $\mu g\ kg^{-1}\ h^{-1}$ over 10 min followed by a maintenance infusion of 0.2–2.5 $\mu g\ kg^{-1}\ h^{-1}$ into a peripheral or central vein. Propofol was given undiluted as an infusion of 1–3 $mg\ kg^{-1}\ h^{-1}$, and a bolus dose of 1 $mg\ kg^{-1}$ was given initially if required. Alfentanil was infused at 0.25–1.0 $\mu g\ kg^{-1}\ min^{-1}$ if the patient complained of pain and analgesia was required. The level of sedation was measured and recorded hourly using the Ramsay sedation score[16] and bispectral index[17], and patients were maintained at a Ramsay sedation score >2 by adjustments to the sedative regimen. Bolus doses of atracurium were given to provide muscle relaxation and paracetamol was used as an antipyretic if necessary. No other sedative or analgesic agents were given.

Patients were ventilated mechanically with oxygen-enriched air to attain acceptable blood gases and extubation was undertaken when indicated clinically. The dexmedetomidine infusion could be continued up to a maximum of 24 h and patients were changed to propofol infusions if they still required sedation and ventilation after this time.

Heart rate, arterial pressure, central venous pressure and oxygen saturation measurements were monitored continuously. Blood samples were obtained from all patients immediately on arrival in the ICU and before administration of sedative or analgesic infusions, and 2, 4, 6, 8, 12 and 24 h after commencement of sedative infusions, provided the patient had not been extubated and the sedative infusion had not been discontinued. In addition, after cessation of the infusion, a short ACTH stimulation test was performed in those patients who had received dexmedetomidine; blood samples were collected 30 and 60 min after administration of synthetic ACTH 250 μg i.v. (Synacthen; CIBA-Geigy, Macclesfield, UK). Samples were centrifuged immediately and serum was stored at –70°C, before analysis in duplicate. Serum concentrations of cortisol, ACTH, insulin, growth hormone (GH), prolactin and IL-6 were measured with commercially available enzyme-linked immunoassay (ELISA) kits. Serial glucose measurements were performed immediately on the ICU using a blood gas analyser (ABL 625; Radiometer, Copenhagen, Denmark), which was calibrated and referenced daily. IL-6 measurements were only performed at baseline and 2, 6, 8 and 12 h after admission to the ICU. The lower limits of sensitivity of the assays were 8.3 $nmol\ litre^{-1}$ for cortisol (Milenia Cortisol, Diagnostic Products, CA, USA), 0.27 $pmol\ litre^{-1}$ for ACTH (Active ACTH, Diagnostic Systems Laboratories, London, UK), 0.11 $mIU\ litre^{-1}$ for growth hormone (Medgenix–HGH–EASIA, Biosource, Nivelles, Belgium), 7.6 $mIU\ litre^{-1}$ for prolactin (Fertigenix–PRL–EASIA, Biosource, Nivelles, Belgium), 0.15 $mIU\ litre^{-1}$ for insulin (Medgenix–INS–EASIA, Biosource, Nivelles, Belgium) and 0.70 $pg\ ml^{-1}$ for IL-6 (Quantikine IL-6; R&D systems, Abingdon, UK). Intra- and inter-assay coefficients of variation were 6.9 and 8.0% respectively for cortisol, 8.6 and 6.6% for ACTH, 3.6 and 7.1% for GH, 6.1 and 8.3% for prolactin, 5.3 and 9.8% for insulin, and 4.2 and 6.4% for IL-6. The morning reference range for cortisol was 138–690 $nmol\ litre^{-1}$.

Sample size was determined from previous work, which indicated that with 20 patients there was a power of 90% to detect a 20% decrease in heart rate at a significance level of 5%. Cardiovascular data are shown as mean (SEM) values and comparisons were made by analysis of variance for repeated measures, followed by *post hoc* Bonferroni testing. Other data are shown as median values (interquartile range), and non-parametric analysis was undertaken. Analysis of serial measurements for unequal time points was performed with a two-stage method that used summary measures for cortisol, ACTH, prolactin, insulin and glucose concentrations.[18] The area under the curve was calculated for each

Table 1 Patient and operative characteristics. Summary statistics are reported as median (interquartile range). Patients: D=dexmedetomidine; P=propofol

Patient	Age (yr)	Operation	Operation time (h)	Intra-operative fentanyl requirement (μg)	Duration of ICU sedative infusion (h)	APACHE II
D1	79	Abdominal aortic aneurysm repair	4	700	12	19
D2	59	Hemihepatectomy	12	1850	8	9
D3	79	Nephrectomy(thoraco-abdominal incision)	3	600	6	18
D4	54	Colectomy/partial pancreatectomy (leiomyosarcoma)	5	500	6	10
D5	60	Extended Whipple's procedure	12	1000	24	19
D6	60	Open reduction and fixation of pelvic fracture	4	750	24	8
D7	76	Total gastrectomy, splenectomy, lienorenal shunt	9	550	12	22
D8	35	Oesophagogastrectomy	10	2000	12	14
D9	83	Salpingo-oophorectomy, removal of ovarian tumour and loop ileostomy	6	1000	8	21
D10	70	Abdominal aortic aneurysm repair	3	500	8	18
	65 (20)	Summary statistics	5.5 (6)	725 (425)	10 (7)	18 (9)
P1	51	Abdominal aortic aneurysm repair	4	800	6	17
P2	91	Laparotomy for perforated appendix (aspiration pneumonia)	1	350	12	26
P3	64	Radical hysterectomy	3	700	6	7
P4	69	Abdominal aortic aneurysm repair	4	800	6	20
P5	63	Open reduction and fixation of pelvic fracture	9	1250	12	10
P6	75	Hemihepatectomy	8	1750	12	15
P7	55	Extended Whipple's procedure	12	1000	12	7
P8	72	Abdominal aortic aneurysm repair	6.5	1000	24	16
P9	66	Abdominal aortic aneurysm repair	4	700	24	21
P10	81	Abdominal aortic aneurysm repair	5	500	12	20
	67.5 (12)	Summary statistics	4.5 (4)	800 (300)	12 (6)	16.5 (10)

patient and between-group comparisons were made using the Mann–Whitney *U*-test. Insulin concentrations at several time points were less than the sensitivity of the assay and so data were ranked and the groups compared using the Kruskal–Wallis test. The ratios of IL-6 concentrations at 2, 6, 8 and 12 h relative to baseline were calculated and then compared using the Mann–Whitney *U*-test. $P<0.05$ was accepted as significant. All analysis was carried out using the Statview for Windows software package (version 4.57; Abacus Concepts, Berkeley, CA, USA).

Results

The groups were similar in age, operation time, dose of intra-operative fentanyl, APACHE II score, weight, mortality and duration of sedative infusion in the ICU (Table 1). One patient (patient P2) underwent an emergency operation; the remaining operations were elective procedures. In the dexmedetomidine and propofol groups, the intra-operative fentanyl requirement was 725 (575–1000) and 800 (700–1000) μg respectively and the duration of sedative infusions 10 (8–15) h and 12 (9–15) h. Two patients in the dexmedetomidine group and three patients in the propofol group received sedation for only 6 h because extubation was indicated clinically. Four patients in the dexmedetomidine group and five in the propofol group received sedation for ≥12 h. Two patients (D1, D2) died in the dexmedetomidine group and one (P7) died in the propofol group, on days 14, 17 and 35 respectively after initially recovering well.

Patients receiving propofol infusions required significantly more alfentanil [2.5 (2.2–2.9) mg h^{-1}] than patients receiving dexmedetomidine [0.8 (0.65–1.2) mg h^{-1}] (P=0.004). The median (range) dexmedetomidine infusion rate was 0.86 (0.45–1.06) $\mu g\ kg^{-1}\ h^{-1}$. Sedation was similar in the two groups, as measured by the Ramsay sedation score and the bispectral index (P=0.68 and P=0.32 respectively).

Haemodynamics

Patients receiving dexmedetomidine had significantly lower heart rates compared with the propofol group (P=0.034), but there were no differences in arterial pressure between the two groups (systolic, P=0.6, diastolic P=0.36) (Fig. 1).

Adrenocortical function

No patients receiving dexmedetomidine had serum cortisol concentrations <138 nmol $litre^{-1}$ during the study, but two patients in the propofol group had concentrations <138 nmol $litre^{-1}$ at more than one sampling time. Cortisol concentrations <400 nmol $litre^{-1}$ or <500 nmol $litre^{-1}$ respectively were found in six and seven patients receiving dexmedetomidine, and in seven and nine patients receiving propofol infusions. There were no differences in cortisol (P=0.22) and ACTH concentrations (P=0.74) between the dexmedetomidine and propofol groups. For clarity, median (interquartile range) values of cortisol and ACTH concentrations are shown only for the first 8 h of infusion in the ICU (Fig. 2). Analysis of the cortisol and ACTH concentrations of individual patients showed a

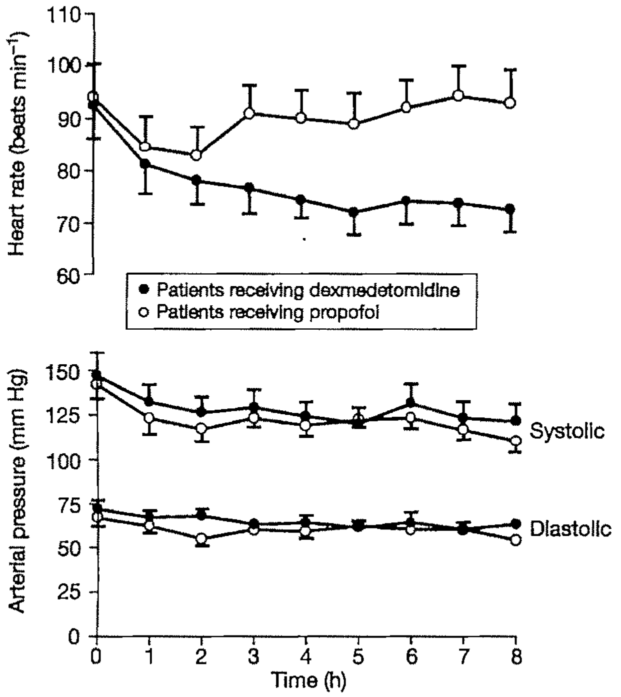

Fig 1 Mean (SEM) heart rate and arterial pressure. n=10 in both groups except at 7 and 8 h, when n=8 and n=7 in the dexmedetomidine and propofol groups respectively.

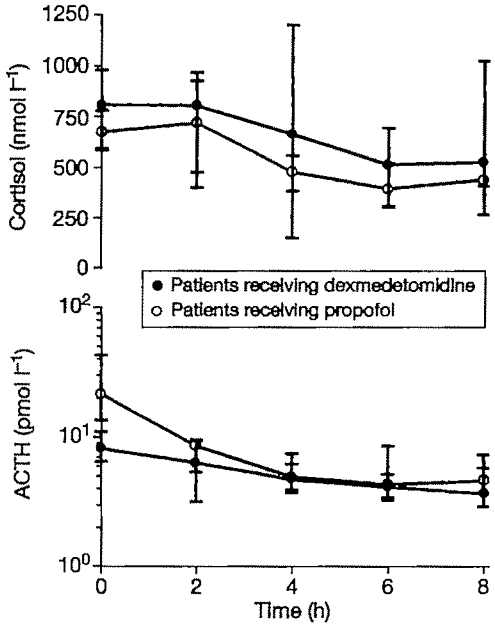

Fig 2 Median (interquartile range) serum cortisol and ACTH. ACTH concentrations are on a logarithmic scale. n=10 in both groups except at 8 h, when n=8 and n=7 in the dexmedetomidine and propofol groups respectively.

normal and appropriate inverse relationship between the two hormones.

Three methods were used for interpreting the short ACTH stimulation test after dexmedetomidine infusion. In the first method, the response to ACTH was considered adequate if the post-ACTH cortisol concentration at 30 or 60 min was >400 nmol litre^{-1}, and in the second method a concentration >550 nmol litre^{-1} was considered adequate. In the third method, if the difference between the pre-ACTH and highest post-ACTH cortisol concentration was >200 nmol litre^{-1}, this was considered an adequate response. Five patients failed the last method, although four of these patients had either high or high normal basal cortisol concentrations. Two patients failed the second method, and one patient failed all three methods for determining an adequate response to ACTH (Table 2).

Endocrine and inflammatory changes (Table 3)

Cortisol and ACTH data are reported above. There were no significant between- or within-group differences in prolactin and glucose concentrations (P=0.25 and P=0.22 respectively).

Two patients in the propofol group and one receiving dexmedetomidine required an insulin infusion to control blood glucose concentration and so were excluded from the analysis of the insulin results. Of the remainder, three patients in the dexmedetomidine group and one patient in the propofol group had insulin concentrations below the sensitivity of the ELISA assay for the whole study period. Insulin concentrations were consistently lower in the dexmedetomidine group, but this was statistically significant only at 2 h (P=0.021).

Serum concentrations of GH increased from baseline in patients receiving dexmedetomidine in the ICU, although this rise was not statistically significant. There was no significant change in the propofol group. There was a statistically significant difference between the groups overall for GH secretion (P=0.036) (Table 3).

Interleukin-6 response

Serum IL-6 concentrations were similar at baseline in the two groups, and patients receiving dexmedetomidine showed a decrease in IL-6 concentrations during the study, in contrast to patients receiving propofol (Table 3). However, there were no statistically significant differences between the dexmedetomidine and propofol groups throughout the study.

Discussion

The results show clearly that there were no differences in serum cortisol or ACTH concentrations between patients receiving post-operative propofol or dexmedetomidine infusions in the ICU (Fig. 2). Propofol infusions have been shown previously to have no significant effects on adrenal steroidogenesis in critically ill patients,[19] and the findings from our study imply that dexmedetomidine acts similarly. There were no differences in the doses of fentanyl given intra-operatively (Table 1), and although fentanyl

Table 2 Assessment of adrenocortical function using three different criteria to interpret the short ACTH stimulation test in patients who had received dexmedetomidine infusions. +=pass, –=fail

Patient	Total dexmedetomidine dose (μg kg^{-1})	Method 1: peak cortisol >400 nmol litre^{-1}	Method 2: peak cortisol >550 nmol litre^{-1}	Method 3: cortisol incremental rise >200 nmol litre^{-1}
1	12.6	+	+	+
2	6.4	+	+	–
3	6.2	+	+	–
4	5.4	+	+	+
5	14.8	+	+	+
6	12.8	+	–	–
7	12.9	+	+	+
8	11.4	–	–	–
9	8.2	+	+	–
10	10.3	+	+	+

Table 3 Median (interquartile range) blood glucose, serum insulin, prolactin, GH and IL-6 concentrations in patients infused with dexmedetomidine (D) or propofol (P). D *vs* P refers to between-group differences determined by estimation of the area under the curve. There was a significant difference in insulin concentrations between the groups at 2 h (*P*=0.021). *n*=10 in both groups except at 8 h, when *n*=8 and *n*=7 in the dexmedetomidine and propofol groups respectively for all measurements, apart from insulin, when *n*=7 and *n*=6 respectively

		Baseline	2 h	4 h	6 h	8 h	D *vs* P
Glucose	D	6.8 (6.1–7.0)	6.1 (5.7–8.6)	7.4 (6.1–8.7)	7.6 (6.0–8.0)	6.3 (5.9–7.9)	*P*=0.22
(mmol litre^{-1})	P	6.9 (5.6–7.7)	7.1 (6.4–7.8)	6.8 (6.1–7.7)	7.0 (6.0–7.5)	6.5 (6.0–7.5)	
Insulin	D	0.15 (0–0.15)	0* (0–3.7)	3.7 (0–4.4)	4.0 (0–4.7)	0.15 (0–13.0)	*P*=0.12
(mU litre^{-1})	P	10.6 (5.7–15.2)	10.4* (4.6–15.7)	10.9 (2.9–17.5)	12.0 (2.9–17.5)	8.2 (3–17.2)	
Prolactin	D	352 (177–464)	196 (135–480)	120 (79–391)	192 (135–332)	205 (101–438)	*P*=0.25
(mU litre^{-1})	P	488 (308–603)	413 (287–485)	321 (218–524)	318 (207–385)	405 (176–423)	
GH	D	4.3 (3.0–5.8)	6.4 (2.9–10.0)	8.7 (4.9–13.6)	7.8 (4.3–10.5)	8.4 (4.4–9.8)	*P*=0.04
(mU litre^{-1})	P	1.5 (1.0–2.2)	0.9 (0–1.4)	0.6 (0–1.1)	1.4 (0–3.9)	3.5 (0.8–5.1)	
IL-6	D	404 (232–595)	385 (354–526)		301 (162–369)	249 (165–354)	*P*=0.36
(pg ml^{-1})	P	286 (178–524)	251 (149–478)		388 (208–428)	527 (461–700)	

may attenuate the endocrine responses to surgery,[20 21] this only occurs at doses much greater than those used in this study. Patients receiving propofol for sedation required significantly more alfentanil in the ICU, but this is unlikely to have influenced the endocrine changes because opioids are unable to attenuate an established cortisol response.[22]

Imidazole compounds are potent, non-selective inhibitors of cytochrome P450 enzymes, through the binding of the unhindered nitrogen in the imidazole ring to the catalytic haem iron atom of the protoporphyrin in the resting cytochrome P450 enzyme.[23] Dexmedetomidine does not inhibit cytochrome P450 enzymes, including those involved in steroidogenesis, at therapeutic concentrations.[4 6] It is difficult to show that a new drug does not affect adrenocortical function in the critically ill because many other factors may be influencing steroidogenesis, including the pathology and other medications. A single test of adrenal function in the ICU remains elusive, and so we assessed steroidogenesis by measuring sequential cortisol and ACTH concentrations and by performing an adrenal cortex stimulation test at the end of the dexmedetomidine infusion.

Hypocortisolism, defined as a serum cortisol concentration below the lower limit of the normal range (<138 nmol litre^{-1}), is probably an inappropriate definition for patients in the ICU. Because surgery, intercurrent illness and ICU interventions will stimulate the hypothalamic–pituitary–adrenal axis, various investigators have suggested lower cortisol limits of 400 or 500 nmol litre^{-1} to be appropriate measures of adrenal insufficiency in these patients.[24] The majority of patients studied would fall into this category at some time in the ICU, a finding reported recently in other ICU patients.[25] These authors concluded that relative dysfunction of the adrenal glands is a frequent occurrence in the ICU patient, although it is unclear what an appropriate circulating cortisol value is in these patients. The exaggerated ACTH response at low concentrations of cortisol seen with etomidate,[26] implying maximal ACTH secretion in order to overcome complete inhibition of cytochrome P450 enzymes, was not seen in this study.

Our results differ from those of Aho and colleagues, who noted that the cortisol response was attenuated during gynaecological laparoscopy.[6] Pre-operative samples provided baseline cortisol values in this study and were lower than those found in our post-operative patients. It is possible that there were small differences in the endocrine response in the dexmedetomidine group that we were unable to detect with the power of the study; our sample size would be expected to show a 50% change in cortisol values based on Aho's work (α value 0.05, β value 0.8).

An ACTH stimulation test is used clinically to diagnose relative adrenal insufficiency, because isolated normal or high cortisol measurements may not reflect the patient's ability to respond to further physiological stress and low cortisol levels do not necessarily imply functional adrenal insufficiency. However, the usefulness and interpretation of this test in both post-operative[27] and intensive care[7] patients remains controversial. There is no agreement in intensive care medicine on the criteria that should be used in evaluating the changes in cortisol after ACTH stimulation. Therefore, it is not surprising that our patients sedated with dexmedetomidine showed differing pass rates depending on the method used to interpret the test. Five patients failed to show an incremental rise in cortisol >200 nmol litre^{-1} after ACTH stimulation (Table 1), reflecting the inadequacy of this criterion in diagnosing adrenocortical dysfunction. The majority of patients had high normal or high basal cortisol values and the magnitude of the incremental rise was inversely proportional to the basal cortisol concentration.[27] It is notable that over 30% of healthy volunteers failed to meet this criterion in one study.[28] There are several criteria in the literature for diagnosing adrenal hypofunction based on the peak cortisol concentration after ACTH stimulation.[27] We chose the lowest value (400 nmol litre^{-1}) and a commonly used value (550 nmol litre^{-1}). Two patients failed to meet two of our selected criteria, but both these patients had an uneventful post-operative ICU and hospital recovery with no clinical suspicion of adrenocortical insufficiency.

Dexmedetomidine failed to modulate the remaining hormonal response to surgery, with the exception of a transient decrease in insulin and augmentation of GH secretion. Alpha-2 adrenoceptor agonists can cause hyperglycaemia in humans[12 29] and even the wild boar.[30] The mechanism is thought to involve postsynaptic α_2-adrenoceptor stimulation of pancreatic beta cells, which inhibits insulin release, although activation of hepatic glycogenolysis and an increase in GH may be involved.[31] Hyperglycaemia was not found after surgery when oral clonidine was given,[32] and this may reflect attenuation of the sympathoadrenal response. We found no differences in glucose concentrations between the groups, and there were no differences in the requirements for exogenous insulin infusion.

Agonists of the α_2-adrenoceptor, including dexmedetomidine, are known to stimulate GH secretion.[5] Increased protein turnover and a negative nitrogen balance are characteristic features of patients in the ICU, and this may prolong ventilation as a result of respiratory muscle weakness and delay mobility. This may be attributable partly to resistance to GH and the decreased production and action of insulin-like growth factor.[33] It was thought that GH therapy may be beneficial in the critically ill, but a recent large multicentre study showed that mortality was increased at least two-fold by the use of large doses of GH in these patients.[34] We found an increase in GH in the dexmedetomidine group that was within the physiological range, and this may be advantageous for patients in the ICU.

Dexmedetomidine may influence the inflammatory response and there is some evidence that this has a beneficial effect on outcome.[9] IL-6 is the principal cytokine released after surgery, and the response is modulated partly by endogenous corticosteroids.[35] In this study, any interaction between IL-6 and cortisol would have been similar in the two groups. Circulating IL-6 concentrations reflect the inflammatory response to surgical trauma, and the similarity of baseline concentrations indicates that the severity of surgery was equivalent in the groups. IL-6 usually peaks about 12 h after surgery,[8] and it is notable that patients receiving dexmedetomidine showed a continuing decline in IL-6 concentrations (Table 3). The lack of a statistically significant difference between the groups may be the result of the small sample size, and further investigation is warranted. According to our results, a sample size of 40 would have an 80% power of detecting a 50% difference in IL-6 (α value 0.05).

In conclusion, dexmedetomidine infusions did not inhibit adrenal steroidogenesis when used for short-term sedation in intubated and ventilated post-operative patients in the ICU. Dexmedetomidine attenuated the heart rate response to surgical trauma compared with propofol and may decrease the inflammatory response to surgical trauma. However, dexmedetomidine had only minor effects on the other endocrine changes.

References

1 Watt I, Ledingham I. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia* 1984; **39**: 973–81

2 Absalom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24h after a single dose of etomidate. *Anaesthesia* 1999; **54**: 861–67

3 Venn R, Bradshaw C, Spencer R, Brealey D, Caudwell E, Naughton C, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54**: 1136–42

4 Maze M, Virtanen R, Daunt D, Banks SJ, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole sedative–anesthetic agent, on adrenal steroidogenesis: in vivo and *in vitro* studies. *Anesth Analg* 1991; **73**: 204–8

5 Kallio A, Scheinin M, Koulu M, Ponkilainen R, Ruskoaho H, Viinamaki O, *et al.* Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. *Clin Pharmacol Ther* 1989; **46**: 33–42

6 Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. *Anesth Analg* 1992; **75**: 932–9

7 Masterson GR, Mostafa SM. Adrenocortical function in critical illness. *Br J Anaesth* 1998; **81**: 308–10

8 Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–17

9 Kennedy BC, Hall GM. Neuroendocrine and inflammatory aspects of surgery: do they affect outcome? *Acta Anaesthiol Belg* 1999; **50**: 205–9

10 Lal S, Tolis G, Martin JB, Brown GM, Guyda H. Effects of clonidine on growth hormone, prolactin, luteinising-hormone, follicle-stimulating hormone and thyroid-stimulating hormone in the serum of normal men. *J Clin Endocrinol Metab* 1975; **41**: 827–32

11 Helbo-Hansen S, Fletcher R, Lundberg D, Nordstrom I, Werner O, Stahl E, *et al.* Clonidine and the sympathoadrenal response to coronary artery by-pass surgery. *Acta Anaesthesiol Scand* 1986; **30**: 235–42

12 Lyons FM, Bew S, Sheeran P, Hall GM. Effects of clonidine on the pituitary hormonal response to pelvic surgery. *Br J Anaesth* 1997; **78**: 134–7

13 Novak-Jankovic V, Paver-Eren V, Bovill JG, Ihan A, Osredkar J. Effect of epidural and intravenous clonidine on the neuro-endocrine and immune stress response in patients undergoing lung surgery. *Eur J Anaesthesiol* 2000; **17**: 50–6

14 Straub RH, Herrmann M, Berkmiller G, Frauenholz T, Lang B, Scholmerich J, *et al.* Neuronal regulation of interleukin 6 secretion in murine spleen: adrenergic and opioidergic control. *J Neurochem* 1997; **68**: 1633–9

15 Dorman T, Clarkson K, Rosenfield BA, Shanholtz C, Lipsett PA, Breslow MJ. Effects of clonidine on prolonged postoperative sympathetic response. *Crit Care Med* 1997; **25**: 1147–52

16 Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *Br Med J* 1974; **2**: 656–9

17 Venn R, Cusack RJ, Rhodes A, Grounds RM. Monitoring the depth of sedation in the intensive care unit. *Clin Intensive Care* 1999; **10**: 81–90

18 Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *Br Med J* 1990; **300**: 230–5

19 Aitkenhead AR, Pepperman ML, Willatts SM, Coates PD, Park GP, Bodenham AR, *et al.* Comparison of propofol and midazolam for sedation in critically ill patients. *Lancet* 1989; **2**: 704–9

20 Klingstedt C, Giesecke K, Hamberger B, Jarnberg PO. High and low dose fentanyl anaesthesia; circulatory and plasma catecholamine responses during cholecystectomy. *Br J Anaesth* 1987; **59**: 184–8

21 Hall GM, Young C, Holdcoft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia* 1978; **33**: 924–30

22 Bent JM, Paterson JL, Mashiter K, Hall GM. Effects of high-dose fentanyl anaesthesia on the established metabolic and endocrine response to surgery. *Anaesthesia* 1984; **39**: 19–23

23 Testa B, Jenner P. Inhibitors of cytochrome P-450s and their mechanism of action. *Drug Metab Rev* 1981; **12**: 1–118

24 Jacobs HS, Nabarro JDN. Plasma 11-hydroxycorticosteroid and growth hormone levels in acute medical illnesses. *Br Med J* 1969; **2**: 595–8

25 Rydvall A, Brandstrom A-K, Banga R, Asplund K, Backlund U, Stegmayr BG. Plasma cortisol is often decreased in patients treated in an intensive care unit. *Intensive Care Med* 2000; **26**: 545–1

26 Fragen RJ, Shanks CA, Molteni A, Avram MJ. Effects of etomidate on hormonal responses to surgical stress. *Anesthesiology* 1984; **61**: 652–56

27 Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation. *Anaesthesia* 1998; **53**: 1091–4

28 Speckart PF, Nicoloff JT, Bethune JE. Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med* 1971; **128**: 761–3

29 Swislocki AL, Vestal RE, Reaven GM, Hoffman BB. Acute metabolic effects of clonidine and adenosine in man. *Horm Metab Res* 1993; **25**: 90–5

30 Wolkers J, Wensing T, Groot Bruinderink GW. Sedation of wild boar (*Sus scrofa*) and red deer (*Cervus elaphus*) with medetomidine and the influence on some haematological and serum biochemical variables. *Vet Q* 1994; **16**: 7–9

31 Angel I, Bidet S, Langer SZ. Pharmacological characterization of the hyperglycemia induced by alpha-2 adrenoceptor agonists. *J Pharmacol Exp Ther* 1988; **246**: 1098–103

32 Nishina K, Mikawa K, Maekawa N, Shiga M, Obara H. Effects of oral clonidine premedication on plasma glucose and lipid homeostasis associated with exogenous glucose infusion in children. *Anesthesiology* 1998; **88**: 922–7

33 Timmins AC, Cotterill AM, Hughes SC, *et al.* Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and an induction of an insulin-like growth factor binding protein 3 protease. *Crit Care Med* 1996; **24**: 1460–6

34 Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341**: 785–92

35 Jameson P, Desborough JP, Bryant AE, Hall GM. The effect of cortisol suppression on interleukin-6 and white blood cell responses to surgery. *Acta Anaesthesiol Scand* 1997; **41**: 304–8

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Does the optimization of cardiac output by fluid loading increase splanchnic blood flow?

S. G. Sakka*, K. Reinhart and A. Meier-Hellmann

Department of Anaesthesiology and Intensive Care Medicine, Friedrich-Schiller-University of Jena, Bachstrasse 18, D-07740 Jena, Germany

**Corresponding author*

We studied the effects of increasing cardiac output by fluid loading on splanchnic blood flow in patients with haemodynamically stabilized septic shock. Eight patients (five female, 39–86 yr) were assessed using a transpulmonary thermo-dye-dilution technique for the measurement of cardiac index (CI) intrathoracic blood volume (ITBV) as a marker of cardiac preload and total blood volume (TBV). Splanchnic blood flow was measured by the steady state indocyanine-green technique using a hepatic venous catheter. Gastric mucosal blood flow was estimated by regional carbon dioxide tension ($P\text{R}_{\text{CO}_2}$). Hydroxyethyl starch was infused to increase cardiac output while mean arterial pressure was kept constant. In parallel, mean norepinephrine dosage could be reduced from 0.59 to 0.33 µg kg^{-1} min^{-1}. Mean (SD) TBV index increased from 2549 (365) to 3125 (447) ml m^{-2}, as did ITBV index from 888 (167) to 1075 (266) ml m^{-2} and CI from 3.6 (1.0) to 4.6 (1.0) litre min^{-1} m^{-2}. Despite marked individual differences, splanchnic blood flow did not change significantly neither absolutely (from 1.09 (0.96) to 1.19 (0.91) litre min^{-1} m^{-2}) nor fractionally as part of CI (from 28.4 (19.5) to 24.9 (16.3)%). Gastric mucosal $P\text{R}_{\text{CO}_2}$ increased from 7.7 (2.6) to 8.3 (3.1) kPa. The $P\text{CO}_2$-gap, the difference between regional and end-tidal $P\text{CO}_2$, increased slightly from 3.2 (2.7) to 3.4 (3.1) kPa. Thus, an increase in cardiac output as a result of fluid loading is not necessarily associated with an increase in splanchnic blood flow in patients with stabilized septic shock.

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Adequate fluid resuscitation is of primary importance in all critically ill patients. During fluid resuscitation of patients with sepsis or septic shock, optimization of global haemodynamics is generally established by a sufficient cardiac preload to gain an optimal cardiac output. Vasopressors should only be used after adequate fluid resuscitation, and then only in the lowest doses necessary.[1] Any increase in cardiac preload which is associated with an increase in cardiac output may enable reduction of vasopressor support. However, it has not yet been established whether an optimization of cardiac preload by fluid loading will actually improve regional blood flow, especially in the splanchnic region.

Partitioning of blood flow to various regional vascular beds is still an important issue in sepsis.[2–4] It is now well known that global parameters do not necessarily reflect regional oxygenation and perfusion. Consequently, guidance of fluid resuscitation by indicators of regional blood flow, especially to those areas that are involved in the outcome from sepsis, has been proposed.[1] Thus, we designed the present study to investigate whether an increase in cardiac output via fluid loading during a decrease in norepinephrine infusion (maintaining mean arterial pressure constant) could improve splanchnic blood flow and oxygenation in patients with septic shock.

Patients and methods

We prospectively studied eight patients (five female, 39–86 yr) with abdominal sepsis and septic shock as defined according to the criteria of the ACCP-SCCM consensus conference.[5] Patient characteristics are shown in Table 1.

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Patients were sedated with fentanyl (0.4–0.6 mg h^{-1}) and droperidol (5.0–7.5 mg h^{-1}). If necessary, midazolam up to 9 mg h^{-1} was administered. In each patient, doses of sedative remained unchanged during the study period. All patients were mechanically ventilated using a pressure controlled mode (Evita 4®, Draeger Werke, Luebeck, Germany) and positive end-expiratory pressure (PEEP) was adjusted individually according to blood gas monitoring (Pa_{O_2} >9 kPa, Pa_{CO_2} <6.5 kPa). Airway pressures remained unchanged throughout the study. PEEP was between 5 and 12 (mean 9 (SD 2)) cm H_2O and inspiratory peak pressure 18–35 (mean 28 (5)) cm H_2O. In this study, dobutamine dosages were kept constant (range 0.0–11.4, mean 3.7, median 3.6 μg kg^{-1} min^{-1}) and only the vasopressor was reduced to keep mean arterial pressure constant. No other vasopressors were used in this study. In our ICU, we keep mean arterial pressure above 75 mm Hg in septic patients to ensure adequate organ perfusion.

For haemodynamic monitoring in each patient, a 4-French gauge flexible catheter with an integrated thermistor and fibreoptic (Pulsiocath® 4F, PV 2024L, Pulsion Medical Systems, Munich, Germany) was advanced into the infradiaphragmatic aorta via the femoral artery. Transpulmonary thermodilution cardiac output, intrathoracic blood volume (ITBV), extravascular lung water (EVLW), and total blood volume (TBV) were calculated using a computer system (COLD-Z021®, Pulsion Medical Systems, Munich, Germany). In this transpulmonary thermo-dye-dilution technique, two specific indicators are injected simultaneously into the central circulation and detected in the aorta.[6] Each bolus injection used cooled (0–6°C) indocyanine-green (ICG) (Pulsion Medical Systems, Munich, Germany) in a concentration of 2 mg ml^{-1} (15 ml per bolus). As cardiac output is one determinant for the calculation of ITBV and EVLW, cardiac output results from the double-indicator injection were verified by single transpulmonary thermodilution, for example each bolus of cooled ICG was followed by two injections of cooled saline. All bolus injections were manual and not ventilator-triggered.

Arterial and hepatic venous blood gas samples were analysed immediately for measurement of oxygen and carbon dioxide tensions, pH, haematocrit, haemoglobin concentration, haemoglobin oxygen saturation, glucose and lactate concentrations (Radiometer System 625®, Copenhagen, Denmark).

A hepatic venous catheter (7.5 French gauge five-lumen pulmonary artery catheter, Edwards Swan Ganz®, CCO/SvO$_2$, Model 744H 7.5 F, Baxter Healthcare Corporation, Irvine, CA, USA) was inserted from the right internal jugular vein under fluoroscopic control for continuous measurement of oxygen saturation (Sv_{O_2}) and assessment of splanchnic blood flow. The correct hepatic venous position of the catheter was verified before and after each study by x-ray.

Pressures were measured with patients in the horizontal position and connected to the ventilator. Besides continuous monitoring of arterial and liver venous arterial pressures, haemodynamic monitoring included measurement of central venous pressure, ITBV index (ITBVI), TBV index (TBVI), and transpulmonary thermodilution cardiac index (CI).

Splanchnic blood flow was evaluated by the steady state ICG (Pulsion Medical Systems, Germany) dye technique. Plasma ICG concentrations were measured spectrophotometrically at a wavelength of 805 nm. Hepatic ICG extraction (*E*) was calculated as described by Uusaro and colleagues.[7] Gastric mucosal $P\mathrm{R}_{CO_2}$ was measured with a 16-French guage tonometric probe (Trip® NGS catheter, Tonometrics Division, Helsinki, Finland). No patient received enteral nutrition or antacids during the study period. Furthermore, neither H_2-inhibitors nor proton pump inhibitors were given during the study. Because of a Boerhaave syndrome in patient 5, $P\mathrm{R}_{CO_2}$ was not obtained in this patient. After conversion of arterial oxygen-partial pressure from [kPa] to [mm Hg], systemic oxygen delivery (Do_2I) was calculated as Do_2I=(haemoglobin concentration ×oxygen saturation×1.36+oxygen partial pressure× 0.0031)×CI. Systemic oxygen consumption (Vo_2I was measured using a metabolic cart (Deltatrac II®, Datex-Engstroem, Helsinki, Finland). In patient 1, no calorimetric data could be obtained because of technical problems.

After an initial ICG bolus of 30 mg, a continuous ICG infusion was started (37.5 mg h^{-1}). After 20, 25, and 30 min of infusion, arterial and hepatic venous blood samples were taken to confirm steady-state ICG concentrations. After 30

Table 1 Patient characteristics. NOR (baseline)=norepinephrine dosage at baseline; NOR (2 h)=norepinephrine dosage after fluid loading; SAPS II=Simplified Acute Physiology Score II; SOFA=Sepsis-related Organ Failure Assessment

Patient	Sex	Age (yr)	Disease	NOR (baseline) (μg kg^{-1} min^{-1})	NOR (2 h) (μg kg^{-1} min^{-1})	SAPS II	SOFA	Outcome
1	F	80	Gastric perforation	0.25	0.12	40	12	Survived
2	F	86	Caecal perforation	0.94	0.55	47	12	Died
3	M	56	Peritonitis, acute cholecystitis	0.27	0.13	47	14	Died
4	F	70	Small intestine infarction	1.89	0.89	53	13	Survived
5	M	46	Perforated gastric ulcer	0.22	0.11	27	14	Died
6	F	39	Perforated duodenal ulcer	0.42	0.33	48	13	Survived
7	F	39	Small intestine perforation	0.25	0.12	48	13	Died
8	M	77	Sigmoid colon perforation	0.50	0.30	46	15	Died

Table 2 Global haemodynamic and oxygen transport variables (n=8). Pa_{O_2}=arterial oxygen tension; FI_{O_2}=inspiratory oxygen fraction. Values for norepinephrine dosages at baseline and after 2 h are presented as mean (median) and 25th–75th percentiles. Differences are presented as mean (SD) [median] and range. P-values are derived from Wilcoxon signed rank test. *Indicates significance ($P < 0.05$)

	Baseline (SD) **[median]**	**2 h** (SD) **[median]**	**Change** (SD) **[median]**	***P*-value**
Heart rate [beats min^{-1}]	103 (12)	97 (14)*	–6 (7) [–5] –22 to 1	0.016
Systolic arterial pressure [mm Hg]	122 (5)	127 (6)	4 (6) [4] –2 to 16	0.11
Diastolic arterial pressure [mm Hg]	62 (10)	60 (9)	–3 (3) [–3] –8 to 2	0.11
Mean arterial pressure [mm Hg]	81 (8)	82 (7)	1 (3) [1] –2 to 6	0.31
Central venous pressure [mm Hg]	9 (3)	12 (4)*	3 (3) [3] 0 to 7	0.016
Intrathoracic blood volume index [ml m^{-2}]	888 (167)	1075 (266)	187 (129) [132] 63 to 378	0.15
CI [litre min^{-1} m^{-2}]	3.6 (1.0)	4.6 (1.0)*	0.9 (0.4) [0.8] 0.6 to 1.5	0.008
Stroke volume index [ml m^{-2}]	58 (12)	77 (9)*	19 (7) [21] 10 to 28	0.008
Total blood volume index [ml m^{-2}]	2549 (365)	3125 (447)*	576 (351) [542] 33 to 1146	0.008
Extravascular lung water index [ml kg^{-1}]	11.8 (4.2)	10.9 (3.9)	–0.9 (1.4) [–0.9] –3.1 to 1.1	0.15
Pa_{O_2} [kPa]	12.6 (4.5)	13.0 (4.7)	0.4 (0.7) [0.5] –0.6 to 1.4	0.20
FI_{O_2} [%]	35 (3)	35 (4)	0.6 (1.8) [0] 0 to 5	1.0
Minute volume [litre min^{-1}]	8.5 (0.9)	7.9 (1.1)*	–0.6 (0.5) [–0.6] –1.5 to 0.1	0.016
Systemic oxygen delivery [ml min^{-1} m^{-2}]	576 (173)	645 (181)*	70 (44) [69] 14 to 150	0.008
Systemic oxygen consumption [ml min^{-1} m^{-2}]	152 (38)	161 (35)*	9 (7) [9] 1 to 20	0.016
Haemoglobin concentration [g dl^{-1}]	11.9 (1.0)	10.5 (0.9)*	–1.3 (0.9) [–1.4] –2.6 to –0.2	0.008
Haematocrit [%]	36.8 (3.6)	32.6 (3.3)*	–4.3 (2.7) [–4.4] –7.7 to –0.6	0.008
Arterial lactate concentration [mmol $litre^{-1}$]	2.4 (0.9)	2.3 (0.7)	–0.1 (0.3) [–0.2] –0.5 to –0.5	0.38
Arterial glucose concentration [mmol $litre^{-1}$]	9.6 (3.2)	9.7 (3.4)	0.1 (1.2) [–0.3] –1.6 to 2.0	0.64
Norepinephrine [µg kg^{-1} min^{-1}]	0.59 [0.35] 0.25–0.72	0.33 [0.22]* 0.12–0.44	–0.26 [–0.14] –0.09 to –0.91	0.008

min of ICG infusion, baseline haemodynamic measurements were made. Then, fluid resuscitation was started by the infusion of 200 kD hydroxyethylstarch 10% (HAES 10 steril®, Fresenius AG, Bad Homburg, Germany) at a rate of 10 ml kg^{-1} over 90 min. To maintain haemoglobin concentration above 10 g dl^{-1}, each patient received 1 unit (300 (30) ml) of packed red blood cells during the study period. The norepinephrine dosage was reduced in each patient and was adjusted individually to keep mean arterial pressure constant. The study period was 2 h.

All results are expressed as mean and standard deviation (SD). For inter-individual comparison, values were normalized by body surface area according to DuBois. Changes between time points were compared using the non-parametric Wilcoxon signed rank test. Statistical significance was considered at $P<0.05$. Associations between measurements are demonstrated using scattergrams and Pearson correlation coefficients (r). For the statistical analysis, we used SigmaStat® for Windows (version 1.0) which was installed on a Compaq® Armada 1590DT computer with a Pentium processor and Microsoft Windows® 95 system.

Results

Mean (SD) Simplified Acute Physiology (SAPS II) Score[8] was 48 (9) and Sepsis-related Organ Failure Assessment (SOFA) score[9] was 13 (1). Global and regional splanchnic haemodynamic and oxygenation variables are summarized in Tables 2 and 3. On average, 756 (281) ml of hydroxyethylstarch were infused, which led to a significant increase in TBV. Haemoglobin concentration decreased significantly from 11.9 (1.0) to 10.5 (0.9) g dl^{-1} and haematocrit from 36.8 (3.6) to 32.6 (3.3)%. As we maintained mean arterial pressure constant, mean norepi-

Table 3 Regional splanchnic haemodynamic and oxygen transport variables (n=8). Differences are presented as mean (SD) [median] and range. P-values are derived from Wilcoxon signed rank test. *Indicates significance ($P < 0.05$). P_{RCO_2}=gastric mucosal CO_2 tension, $P_{E'CO_2}$=end-expiratory CO_2 tension

	Baseline (SD)	**2 h (SD)**	**Change (SD) [median]**	***P*-value**
Splanchnic blood flow [litre min^{-1} m^{-2}]	1.09 (0.96)	1.19 (0.91)	0.10 (0.24) [0.02] –0.26 to 0.40	0.38
Fractional splanchnic blood flow [%]	28.4 (19.5)	24.9 (16.3)	–3.5 (6.8) [–2.8] –0.3 to 1.1	0.25
Splanchnic O_2 delivery [ml min^{-1} m^{-2}]	155 (107)	175 (150)	20 (61) [9] –57 to 146	0.55
Splanchnic O_2 consumption [ml min^{-1} m^{-2}]	74 (51)	66 (35)	–8 (28) [1] –44 to 21	0.64
Splanchnic O_2 extraction ratio [%]	51.7 (21.9)	46.6 (16.1)	–5.1 (8.2) [–4.8] –16.1 to 8.6	0.15
Hepatic venous O_2 saturation [%]	48.0 (21.8)	52.4 (16.9)	4.4 (8.2) [5.2] –7.3 to 17.6	0.20
ICG clearance [ml min^{-1} m^{-2}]	181 (72)	168 (89)	–14 (107) [25] –269 to 51	0.46
Hepatic venous lactate concentration [mmol $litre^{-1}$]	2.0 (1.0)	2.0 (0.9)	0.0 (0.4) [0] –0.5 to 0.6	0.84
Hepatic venous glucose concentration [mmol $litre^{-1}$]	9.7 (3.6)	9.5 (3.4)	–0.1 (1.1) [–0.1] –1.9 to 1.3	0.74
P_{RCO_2} [kPa]	7.7 (2.6)	8.3 (3.1)*	0.6 (0.7) [0.4] 0.0 to 2.0	0.03
$P_{E'CO_2}$ [kPa]	4.6 (0.7)	5.0 (0.8)	0.4 (0.4) [0.3] 0.0 to 1.0	0.06
P_{CO_2}-gap [kPa]	3.2 (2.7)	3.4 (3.1)	0.2 (0.6) [0.3] –0.7 to 1.3	0.38

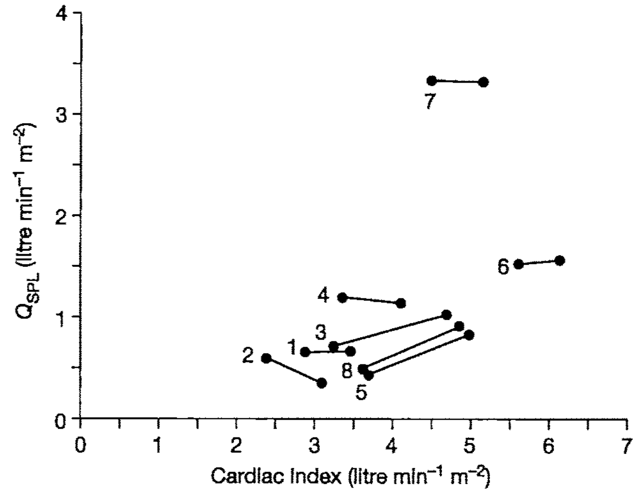

Fig 1 CI and absolute splanchnic blood flow in eight patients undergoing fluid loading associated with an increase in cardiac output during constant mean arterial pressure. Q_{SPL}=splanchnic blood flow.

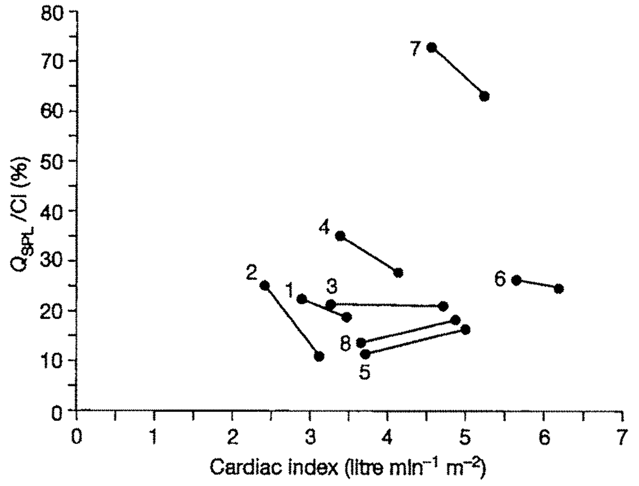

Fig 2 CI and fractional splanchnic blood flow as part of CI in eight patients undergoing fluid loading associated with an increase in cardiac output during constant mean arterial pressure. Q_{SPL}=splanchnic blood flow; CI = Cardiac index.

nephrine dosage was reduced during fluid loading (from 0.59 to 0.33 µg kg^{-1} min^{-1}). Over all eight patients, mean heart rate decreased from 103 (12) to 97 (14) beats min^{-1}. CI increased from 3.6 (1.0) to 4.6 (1.0) litre min^{-1} m^{-2} and stroke volume index increased significantly from 58 (12) to 77 (9) ml m^{-2}. ITBVI increased from 888 (167) to 1075 (266) ml m^{-2} and central venous pressure from 9 (3) to 12 (4) mm Hg. Total blood volume index increased significantly from 2549 (365) to 3125 (447) ml m^{-2}. Absolute splanchnic blood flow did not change significantly (from 1.09 (0.96) to 1.19 (0.91) litre min^{-1} m^{-2}), nor did fractional splanchnic perfusion as part of CI (from 28.4 (19.5) to 24.9 (16.3%)). Interestingly, the individual data showed that in some patients absolute and fractional splanchnic blood flow even decreased (Figs 1 and 2). Splanchnic blood flow increased most in patients with the greatest increase in CI, r=0.84 (P=0.009) (Fig. 3).

As we used pressure-controlled ventilation, minute volume significantly decreased from 8.5 (0.9) to 7.9 (1.1)

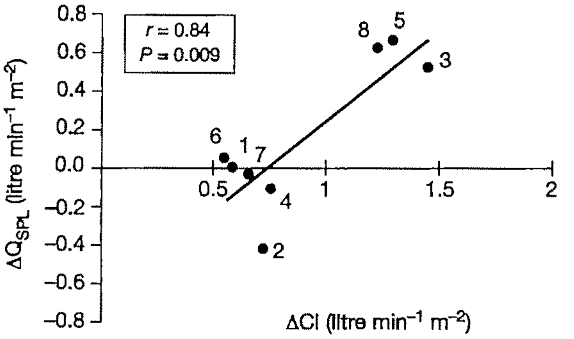

Fig 3 Changes in cardiac index and in splanchnic blood flow in eight patients undergoing fluid loading associated with an increase in cardiac output during constant mean arterial pressure. Q_{SPL}=splanchnic blood flow; CI=cardiac index.

litre min^{-1} while end-expiratory CO_2-tension increased non-significantly from 4.6 (0.7) to 5.0 (0.8) kPa. The difference between regional and end-tidal PCO$_2$ (PCO$_2$-gap) increased slightly from 3.2 (2.7) to 3.4 (3.1) kPa. Steady-state conditions were confirmed by coefficients of variation for ICG concentrations of 4.6 (2.2) and 4.4 (2.4)% for all arterial and hepatic venous samples, respectively.

Discussion

These data demonstrate that, in patients with haemodynamically stabilized septic shock, an increase in cardiac output because of fluid loading associated with reduced vasopressor support—a strategy that has been suggested in recently published recommendations in the treatment of sepsis[1]—does not necessarily lead to an increase in splanchnic blood flow. Moreover, we demonstrated that the response to fluid loading and reduction in vasopressor support is very variable. Indeed splanchnic perfusion was increased with increasing CI in some patients, but in others it was not. More detailed analysis of this non-uniform response showed that splanchnic blood flow increased most in patients with the greatest increase in CI.

Another reason for the heterogeneous effects of fluid loading in our study might also have been that fluid loading did not really increase cardiac preload and consequently cardiac output in all patients. As clearly demonstrated in Figure 1, an increase in cardiac output was observed in every patient. Furthermore, the ratio between ITBV and TBV remained unchanged (35 (4) and 34 (5) %), indicating that fluid loading increased ITBV proportionally. The techniques that we used in this study for the measurement of cardiac preload and cardiac output are well validated. For the measurement of cardiac output we used transpulmonary thermodilution, which has been extensively validated against reference techniques; for example, pulmonary artery thermodilution and Fick principle derived values.[10–16] Furthermore, the transpulmonary double-indicator dilution technique allows the measurement of the ITBV, which has been found to be an appropriate or even better indicator of cardiac preload in critically ill patients when compared with cardiac filling pressures.[17–19]

As PEEP itself may affect splanchnic blood flow and hepatic function[20–22] we maintained airway pressures constant. Droperidol may have influenced splanchnic blood flow, but in our study, droperidol doses remained stable.

Of course, in our study we cannot separate the effects of the two different therapeutic interventions, i.e. fluid loading and reduction in norepinephrine, on splanchnic blood flow. On the other hand, the aim of our study was to mimic clinical practice. In the clinical setting, when perfusion pressure increases after fluid loading, norepinephrine support is normally reduced.

The effects on norepinephrine on splanchnic blood flow cannot be assessed in our study. However, the combination of fluid loading with a reduction in vasopressor support did not always increase splanchnic blood flow. Norepinephrine has been shown to increase splanchnic vascular resistance and, thus, decrease splanchnic blood flow in animal and human studies during non-septic conditions.[23 24] Thus, one could speculate that decreasing vasopressor support should be associated with an increase in splanchnic blood flow. On the other hand, Bersten and colleagues[24] demonstrated that a redistribution of blood flow with norepinephrine infusion, away from the kidneys, liver and pancreas, was not observable in septic animals. Moreover, a beneficial effect of norepinephrine on splanchnic oxygenation, by increasing mean arterial pressure in septic patients, was shown by Marik and colleagues[25] who compared norepinephrine and high-dose dopamine as vasopressors. In their study, dopamine increased mean arterial pressure largely by increasing CI whereas norepinephrine increased mean arterial pressure by increasing systemic vascular resistance while maintaining CI. Although oxygen delivery and oxygen consumption increased in both groups of patients, gastric mucosal pH (pHi)—an indicator of microcirculatory perfusion—increased significantly in those patients treated with norepinephrine whereas pHi decreased significantly in those patients receiving dopamine.

Thus, norepinephrine seems to have potential beneficial effects on splanchnic blood flow in patients with sepsis. By maintaining mean arterial pressure constant while reducing norepinephrine in the present study, we controlled for perfusion pressure alone as the cause of these effects. However, some patients showed a decrease in splanchnic blood flow after optimization of CI.

Variation in responses of septic patients to vasoactive substances has been reported previously.[26 27] In these studies, the effects of norepinephrine and low-dose dopamine on splanchnic blood flow were found to be unpredictable.

In conclusion, we have shown that an increase in cardiac output as a result of fluid loading while keeping mean arterial pressure constant is not necessarily associated with an increase in regional blood flow. Further studies are necessary to better understand this varying response of splanchnic perfusion.

References

1 Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27**: 639–60

2 Russell JA. Catecholamines and the splanchnic circulation. *Crit Care Med* 1999; **27**: 242–3

3 Mythen M. Dopexamine protects the gut mucosa during major surgery? *Crit Care Med* 1999; **27**: 2038–9

4 Marik PE. Splanchnic circulation and the dopexamine paradox. *Crit Care Med* 1999; **27**: 2302–3

5 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74

6 Hoeft A. Transpulmonary indicator dilution: an alternative approach for hemodynamic monitoring. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine 1995*. Berlin: Springer-Verlag, 1995; 593–605

7 Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; **30**: 106–12

8 Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957–63

9 Vincent J-L, Moreno R, Takala J. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/ failure. *Intensive Care Med* 1996; **22**: 707–10

10 Pavek K, Lindquist O, Arfors K-E. Validity of thermodilution method for measurement of cardiac output in pulmonary oedema. *Cardiovasc Res* 1973; **7**: 419–22

11 Wickerts C-J, Jakobsson J, Frostell C, Hedenstierna G. Measurement of extravascular lung water by thermal-dye technique: mechanisms of cardiac output dependence. *Intensive Care Med* 1990; **16**: 115–20

12 Böck JC, Barker BC, Mackersie RC, Tranbaugh RF. Cardiac output measurements using femoral artery thermodilution in patients. *J Crit Care* 1989; **4**: 106–11

13 Lewis FR, Elings VB, Hill SL, Christensen JM. The measurement of extravascular lung water by thermal-green dye indicator dilution. *Ann N Y Acad Sci* 1982; **384**: 394–410

14 Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. *Chest* 1998; **113**: 1070–7

15 Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of pulmonary artery and arterial thermodilution cardiac output in critically ill patients. *Intensive Care Med* 1999; **25**: 843–6

16 Sakka SG, Reinhart K, Wegscheider K, Meier-Hellmann A. Is the placement of a pulmonary artery catheter still justified solely for the measurement of cardiac output? *J Cardiothorac Vasc Anesth* 2000; **14**: 119–24

17 Hoeft A, Schorn B, Weyland A, *et al.* Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; **81**: 76–86

18 Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; **18**: 142–7

19 Sakka SG, Bredle DL, Reinhart K, Meier-Hellmann A. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. *J Crit Care* 1999; **14**: 78–83

20 Winsö O, Biber B, Gustavsson B, Holm C, Milsom I, Niemand D. Portal blood flow in man during graded positive end-expiratory pressure ventilation. *Intensive Care Med* 1986; **12**: 80–5

21 Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic blood flow and performance. *J Appl Physiol* 1987; **62**: 1377–83

22 Kiefer P, Nunes S, Kosonen P, Takala J. Effect of positive end-expiratory pressure on splanchnic perfusion in acute lung injury. *Intensive Care Med* 2000; **26**: 376–83

23 Granger DN, Richardson PDI, Kvietys PR, Mortillaro NA. Intestinal blood flow. *Gastroenterology* 1980; **78**: 837–63

24 Bersten AD, Hersch M, Cheung H, Rutledge FS, Sibbald WJ. The effect of various sympathomimetics on the regional circulations in hyperdynamic sepsis. *Surgery* 1992; **112**: 549–61

25 Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994; **272**: 1354–7

26 Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Jansen EJ. Regional blood flow and oxygen transport in septic shock. *Crit Care Med* 1993; **21**: 1296–1303

27 Meier-Hellmann A, Bredle DL, Specht M, Spies C, Hannemann L, Reinhart K. The effects of low-dose dopamine on splanchnic blood flow and oxygen uptake in patients with septic shock. *Intensive Care Med* 1997; **23**: 31–7

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Amrinone can accelerate the cooling rate of core temperature during deliberate mild hypothermia for neurosurgical procedures

S. Inoue[1]*, M. Kawaguchi[1], T. Sakamoto[1], T. Iwata[1], Y. Kawaraguchi[1], H. Furuya[1] and T. Sakaki[2]

[1]*Department of Anaesthesiology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan.* [2]*Department of Neurosurgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan*

**Corresponding author*

We investigated the effects of i.v. amrinone on intraoperative changes of core temperature during deliberate mild hypothermia for neurosurgery. The patients in a control group (n=10) did not receive amrinone and patients in the amrinone group (n=10) received amrinone 5 $\mu g\ kg^{-1}\ min^{-1}$ after a loading dose of 1.0 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen, propofol and fentanyl. After the induction of anaesthesia, patients were cooled and tympanic membrane temperature was maintained at 34.5°C. After completion of the main surgical procedures, patients were rewarmed in the operating room. Tympanic membrane temperatures between 30 and 90 min after cooling were significantly lower in the amrinone group than in the control group. During cooling, the times taken to cool to 35°C and to the lowest temperature were significantly shorter in the amrinone group than in the control group. These results suggest that i.v. amrinone can accelerate the cooling rate of core temperature during deliberate mild hypothermia for neurosurgical procedures.

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Deliberate mild hypothermia has been proposed as a means of providing cerebral protection during neurosurgical procedures that carry the risk of cerebral ischaemia, such as cerebral aneurysm clipping and arteriovenous malformation resection. Although the effects of mild hypothermia on neurological outcome in such situations are still unknown,[1–3] research into techniques that allow the safe management of intraoperative deliberate mild hypothermia seems warranted.

Vasoconstriction limits the core-to-peripheral redistribution of body heat during cooling and peripheral-to-core heat transfer during rewarming. Several investigators have examined the effects of vasodilating agents, such as prostaglandin E_1, nicardipine and sodium nitroprusside, on cooling and rewarming during deliberate mild hypothermia.[4–6] However, these agents did not affect intraoperative temperature management during deliberate mild hypothermia. Mild hypothermia not only promotes thermoregulatory vasoconstriction[7] but it also decreases cardiac output as a result of depression of left ventricular contractility,[8] which may contribute to poor heat regulation. Therefore, intraoperative temperature management may benefit from inotropic therapy as well as vasodilator therapy.

Amrinone is a phosphodiesterase inhibitor that has inotropic and vasodilatory effects.[9] It has been used in neurosurgery to treat vasospasm after subarachnoid haemorrhage,[10] although its effects on the cerebral circulation are still not fully understood. We tested the hypothesis that the administration of amrinone accelerates the cooling and rewarming rates of core temperature during deliberate mild hypothermia for neurosurgery.

Patients and methods

After institutional approval and informed consent, 20 patients scheduled to undergo elective neurosurgical procedures in the supine position were enrolled. Patients with symptomatic ischaemic heart disease, hepatic disease, renal disease, coagulopathy and patients who were receiving vasodilator medication were excluded. At the commencement of the active cooling, patients with a tympanic membrane temperature greater than 37.0°C or less than 36.0°C were excluded.

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All patients received preoperative medication with a histamine type 2 receptor antagonist (roxatidine 75 mg orally 2 h preoperatively). Anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1}, fentanyl 1–2 µg kg^{-1} and vecuronium 0.15 mg kg^{-1}. The trachea was intubated and the lungs were ventilated mechanically. Anaesthesia was maintained with 50–67% nitrous oxide in oxygen and propofol 3–5 mg kg^{-1} h^{-1}, and supplemented with doses of fentanyl and vecuronium. Additional vecuronium was administered as required to maintain one or two mechanical twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. Routine monitoring included electrocardiogram, a radial arterial catheter, a non-invasive blood pressure cuff, pulse oximetry and capnogram. A tympanic membrane probe consisting of copper–constantan thermocouple sensors (Mallinckrodt Medical, St Louis, MO, USA) was inserted in the external auditory meatus on the side opposite surgery for temperature monitoring. The probe was then taped in place, the aural canal occluded with cotton and the external ear covered with a gauze pad. Adhesive skin temperature probes (Mallinckrodt Medical) were placed on the ventral surface of the forearm and the tip of the index finger.

A water blanket (RK1000; American Medical Systems, Cincinnati, OH, USA) was placed under each patient. A polyurethane formed pad covered with a cotton sheet (S-K pad; Asahi Medical Co., Osaka, Japan) protected the patient from direct contact with the water blanket. A convective warming/cooling blanket (Warm Touch; Mallinckrodt Medical) was applied directly to the ventral body surface. The arm used to monitor the skin temperature was not covered by the convective blanket. After the induction of anaesthesia, active cooling was started. The temperature of the water blanket was set at 5°C and air at room temperature was circulated through the convective blanket. Active cooling was stopped at a tympanic membrane temperature of 35°C and body temperature was then allowed to drift downwards. The temperature settings of the water blanket and the convective blanket were then adjusted to maintain a target tympanic membrane temperature of 34.5°C (passive cooling). After completion of the major surgical procedures, active rewarming was instituted with the water blanket set at 41°C and the convective blanket at its highest setting (43°C). Active rewarming was stopped at a tympanic membrane temperature of 35.5°C, and body temperature was then allowed to drift upwards. The temperature settings on the water blanket and the convective blanket were then adjusted to maintain a target tympanic membrane temperature of 36°C (passive rewarming). After the operation, the patient's trachea was extubated in the operating room.

Patients were assigned randomly to one of two groups; patients in the control group did not receive amrinone, and patients in the amrinone group received with a loading dose of amrinone 1.0 mg kg^{-1} followed by infusion of amrinone 5 µg kg^{-1} min^{-1}. The administration of amrinone was started just after the induction of anaesthesia and continued until the end of anaesthesia. Loading of amrinone was performed over approximately 5–10 min. Temperatures were recorded at 15 min intervals, starting immediately after induction of anaesthesia, when active cooling was started (initial values). Temperature gradients of the skin surface (forearm minus fingertip) were calculated. As in a previous study, we considered a temperature gradient <0°C to indicate vasodilation.[7] Arterial blood samples were analysed for Pa_{O_2}, Pa_{CO_2}, pH, base excess and concentrations of haemoglobin, Na+, K+, glucose and lactate with a commercial blood gas analyser (Chiron 860; Chiron, Tokyo, Japan). Blood samples were collected at the initiation of active cooling and when the target temperature was achieved and were analysed immediately after collection.

Data handling and statistical analysis

Active cooling and rewarming rates (°C h^{-1}) were defined as the slopes of the simple regression lines calculated from plotted core temperature values over time from the beginning of cooling to the time when the temperature reached 35°C, and from the beginning of rewarming to the time when the temperature reached 35.5°C.

Comparisons of changes in haemodynamic variables and temperatures between the two groups were performed by two-way analysis of variance for repeated measures followed by Fisher's protected least significant difference. Other comparisons between the two groups were carried out with the unpaired Student's *t*-test for continuous variables and the χ^2 test for nominal data. The data are expressed as mean (SEM); differences were considered significant with a *P* value of <0.05.

Results

Patient characteristics and the type of surgery are shown in Table 1. Intraoperative changes in tympanic membrane temperature and skin surface temperature gradient (forearm minus fingertip) are shown in Fig. 1. Tympanic membrane temperatures 30–90 min after the start of active cooling were significantly lower in the amrinone group than in the control group. The temperature gradient 30 min after the start of active cooling was significantly lower in the amrinone group than in the control group. By contrast, during the rewarming period, the tympanic membrane temperature and the temperature gradient at each time interval were similar in the two groups. Table 2 shows a comparison of intraoperative variables. The times taken for active cooling to achieve a core temperature of 35°C and the lowest temperature were significantly shorter in the amrinone group than in the control group. The active cooling rate was significantly greater in the amrinone group than in the control group. However, there were no significant group differences in the rewarming time to reach 35.5°C and the rewarming rate. There were no significant differences in anaesthesia and surgery times, total volumes of intravenous infusions, transfusion, blood loss, urinary output and total doses of fentanyl and propofol.

Figure 2 shows the intraoperative changes in heart rate and mean arterial blood pressure. There were no significant differences between the two groups in heart rate at each time interval during the study. The mean arterial blood pressure at the beginning of rewarming was significantly lower in the amrinone group than in the control group.

Table 1 Patient characteristics and indications for surgery. The control group did not receive amrinone; the amrinone group received a loading dose of amrinone 1.0 mg kg^{-1} then an infusion of amrinone 5 μg kg^{-1} min^{-1}. The data are expressed as mean (SEM). OCVD = occlusive cerebrovascular disease

	Control	Amrinone
n	10	10
Age (yr)	51 (4)	57 (3)
Gender (F/M)	5/5	4/6
Weight (kg)	59 (2)	60 (3)
Height (cm)	160 (2)	158 (2)
Disease		
Cerebral aneurysm	2	4
Brain tumour	4	4
OCVD	2	0
Others	2	2

The results of the arterial blood analyses are shown in Table 3. There were no significant differences between the two groups in pH, Pa_{CO_2}, Pa_{O_2}, base excess, haemoglobin, Na+, K+, glucose and lactate before or during mild hypothermia.

Discussion

The results of this study reveal that intraoperative administration of amrinone 5 μg kg^{-1} min^{-1} after a loading dose of 1.0 mg kg^{-1} accelerated the cooling rate of the core temperature, although it did not affect the rewarming rate after deliberate mild hypothermia.

Core hypothermia during general anaesthesia develops with three characteristic phases.[11–13] Initial core hypothermia results from core-to-peripheral redistribution of body heat when anaesthesia inhibits tonic thermoregulatory vasoconstriction. Subsequently, heat loss exceeding metabolic heat production lowers core temperature in a slow, linear fashion. Finally, a core temperature plateau results when the emergence of thermoregulatory vasoconstriction decreases cutaneous heat loss and constrains metabolic heat to the core thermal compartment. We proposed that the combination of the inotropic effect with the vasodilatory

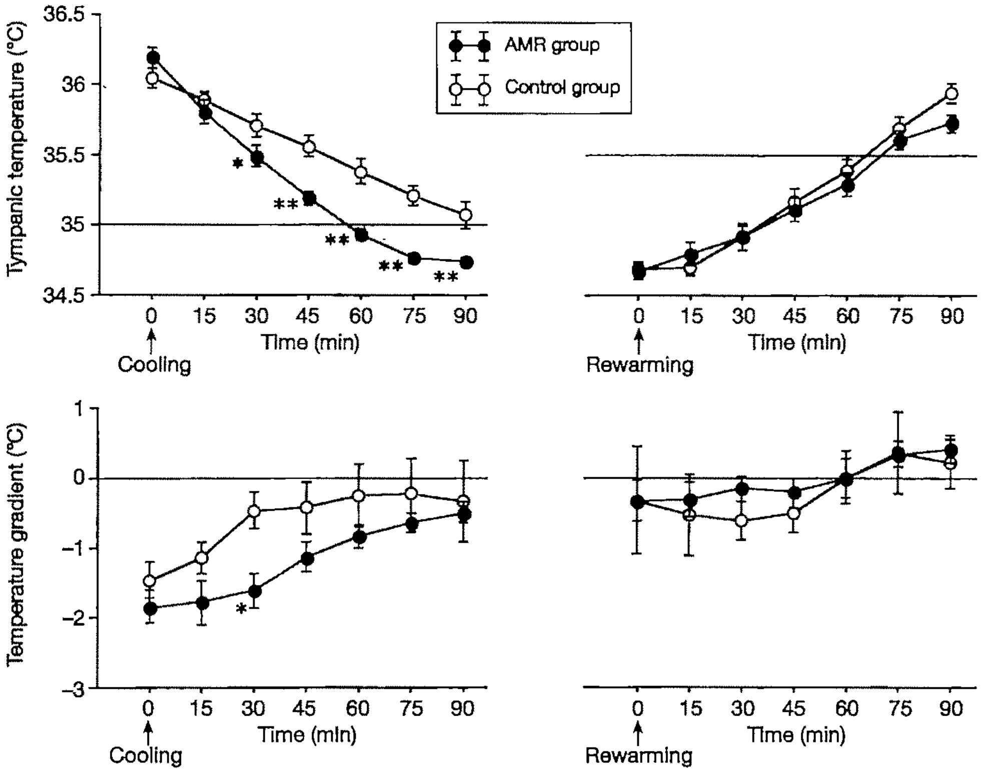

Fig 1 Intraoperative changes in tympanic membrane temperature and skin surface temperature gradient (forearm minus fingertip). Tympanic membrane temperature 30–90 min after cooling was significantly lower in the amrinone (AMR) group than in the control group. The temperature gradient 30 min after the cooling was significantly lower in the amrinone group than in the control group. The amrinone group received a loading dose of amrinone 1.0 mg^{-1} kg^{-1} then an infusion of amrinone 5 μg kg^{-1} min^{-1}; the control group did not receive amrinone. The data are expressed as mean (SEM). Comparisons between the two groups were performed by two-way analysis of variance for repeated measures followed by Fisher's protected least significant difference test. *$P<0.05$ versus control group; **$P<0.01$ versus control group.

effect—the 'inodilatory effect'—of amrinone would enhance the redistribution of body heat and cutaneous heat loss and would inhibit the thermoregulatory vasoconstriction, resulting in an increase in the cooling rate. Just as we had expected, amrinone accelerated the cooling rate of the core temperature during deliberate mild hypothermia in the present study.

Evidence supporting our proposed mechanism was found in the present study. The forearm minus fingertip skin surface temperature gradient became significantly lower in the amrinone group than in the control group before the tympanic membrane temperature became significantly lower in the amrinone group than in the control group. The temperature gradient is considered to be a measure of peripheral thermoregulatory vasoconstriction.[7] [14] [15] Generally, it is considered that the more positive the temperature gradient the greater is the degree of vasoconstriction, whereas the more negative the temperature gradient the greater is the degree of vasodilation. Thus, we suggest that the inodilatory effect of amrinone inhibits thermoregulatory vasoconstriction, promoting the redistribution of body heat and cutaneous heat loss and resulting in acceleration of the cooling rate of core temperature. However, it is uncertain whether the inotropic or the vasodilatory effect is mainly responsible for this effect,

Table 2 Intra-operative variables. The control group did not receive amrinone; the amrinone group received a loading dose of amrinone 1.0 mg kg^{-1} then an infusion of amrinone 5 μg kg^{-1} min^{-1}. The data are expressed as mean (SEM). Comparisons between the two groups were performed with unpaired Student's *t*-test. *Statistically significant difference between the groups ($P<0.05$)

	Control	Amrinone	*P*
Anaesthesia time (min)	360 (27)	324 (41)	0.4809
Surgery time (min)	274 (31)	229 (37)	0.3628
Crystalloid infusion (ml)	2690 (153)	2707.(230)	0.9515
Blood transfusion (ml)	40 (40)	80 (53)	0.5560
Blood loss (ml)	327 (63)	229 (46)	0.2239
Urinary output (ml)	1472 (162)	1526 (202)	0.8368
Total dose of fentanyl (mg)	395 (48)	375 (41)	0.7546
Total dose of propofol (mg)	1345 (88)	1261 (123)	0.5867
Lowest temperature (°C)	34.6 (0.04)	34.6 (0.04)	0.5785
Temperature at extubation (°C)	36.0 (0.1)	35.9 (0.1)	0.4832
Cooling to 35°C (min)*	86 (7)	60 (4)	0.0067
Cooling to lowest temperature (min)*	135 (5)	101 (8)	0.0021
Rewarming to 35.5°C (min)	64 (5)	72 (5)	0.2867
Rewarming to extubation (min)	103 (4)	96 (5)	0.2233
Surgery end to extubation (min)	34 (6)	31 (3)	0.6284
Cooling rate (°C h^{-1})*	-0.74 (0.08)	-1.30 (0.08)	0.0002
Rewarming rate (°C h^{-1})*	0.83 (0.07)	0.73 (0.08)	0.3813

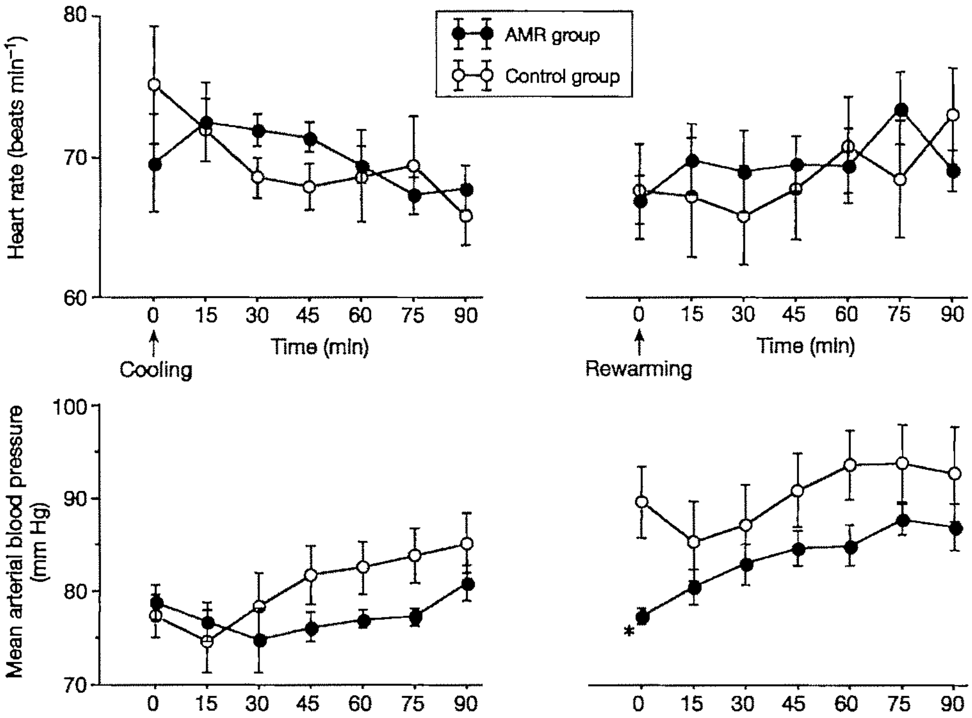

Fig 2 Intraoperative changes in heart rate and mean arterial blood pressure. There were no significant differences between the two groups in heart rate at each time interval during the operation. Mean arterial blood pressure at the beginning of the rewarming was significantly lower in the amrinone (AMR) group than in the control group. There were no significant differences between the two groups in heart rate at each time interval during the operation. The amrinone group received a loading dose of amrinone 1.0 mg^{-1} kg^{-1} then an infusion of amrinone 5 μg kg^{-1} min^{-1}; the control group did not receive amrinone. The data are expressed as mean (SEM). Comparisons between the two groups were performed by two-way analysis of variance for repeated measures followed by Fisher's protected least significant difference test. *$P<0.05$ versus control group; **$P<0.01$ versus control group.

Table 3 Intraoperative arterial blood chemistry variables. The control group did not receive amrinone; the amrinone group received a loading dose of amrinone 1.0 mg kg^{-1} then an infusion of amrinone 5 $\mu g\ kg^{-1}\ min^{-1}$. The data are expressed as mean (SEM). Comparisons between the two groups were performed with unpaired Student's *t*-test. NT = normothermia; HT = hypothermia

	Control	Amrinone	*P*
pH NT	7.47 (0.01)	7.46 (0.01)	0.4656
pH HT	7.44 (0.01)	7.46 (0.01)	0.1533
Pa_{CO_2} (mm Hg) NT	36 (1)	37 (1)	0.4656
Pa_{CO_2} (mm Hg) HT	37 (1)	36 (1)	0.4627
Pa_{O_2} (mm Hg) NT	192 (24)	211 (17)	0.5046
Pa_{O_2} (mm Hg) HT	189 (16)	202 (17)	0.5645
Base excess (mmol $litre^{-1}$) NT	2.3 (0.7)	2.2 (0.5)	0.9038
Base excess (mmol $litre^{-1}$)HT	1.2 (0.7)	1.2 (0.5)	0.8695
Haemoglobin (mg dl^{-1}) NT	11 (1)	11 (0)	0.9279
Haemoglobin (mg dl^{-1}) HT	11 (1)	10 (0)	0.3787
Na+ (mmol $litre^{-1}$) NT	138 (1)	137 (1)	0.5129
Na+ (mmol $litre^{-1}$) HT	136 (2)	135 (1)	0.4417
K+ (mmol $litre^{-1}$) NT	3.6 (0.1)	3.7 (0.2)	0.4559
K+ (mmol $litre^{-1}$) HT	3.7 (0.1)	3.6 (0.1)	0.5495
Glucose (mg dl^{-1}) NT	96 (6)	106 (7)	0.2725
Glucose (mg dl^{-1}) HT	105 (5)	108 (6)	0.6970
Lactate (mmol $litre^{-1}$) NT	1.9 (0.2)	1.6 (0.3)	0.8062
Lactate (mmol $litre^{-1}$) HT	1.8 (0.3)	2.3 (0.5)	0.8380

because we did not measure cardiac output or skin blood flow. Shitara *et al.* demonstrated that dobutamine accelerated the decline of core temperature in volunteers anaesthetized with isoflurane.[16] They attributed this to the inotropic and vasodilatory effects of dobutamine. These results are compatible with our results.

In the present study the rewarming of the core temperature was not influenced by the administration of amrinone. Previous investigators have tested the hypothesis that thermoregulatory vasoconstriction decreases cutaneous transfer of applied heat and restricts peripheral-to-core flow of heat, thereby delaying and reducing the increase in core temperature.[4 6 17] However, rewarming of the core temperature was not affected by vasodilation by anaesthetics, sodium nitroprusside and prostaglandin E_1. We thought that the combined inotropic and vasodilatory effect of amrinone would maintain peripheral circulation and cardiac output, thereby enhancing peripheral heat gain and the peripheral-to-core flow of heat, resulting in an acceleration of the rewarming rate. However, amrinone did not influence the rewarming of the core temperature after deliberate mild hypothermia. The temperature gradient in the two groups showed similar changes during the rewarming phase. The inodilatory effect of amrinone might be modified under mild hypothermic conditions. Alternatively, the dose of amrinone used in this study might have been insufficient to counteract the active vasoconstriction under mild hypothermic conditions. It is interesting to note that postoperative rebound hyperthermia[1] was not observed in this study. This may be because of the passive warming method we used.

Factors known to affect cooling and rewarming include the morphometric characteristics of patients, the presence or absence of vasoconstriction, and the method of temperature management.[18] Intra-operative thermoregulatory vasoconstriction thresholds may be influenced by the depth of anaesthesia, age, and painful stimulation.[19–23] In our study, anaesthesia and the method of temperature management were standardized and the morphometric data were similar in the two groups.

It is possible that higher doses of amrinone might affect the rewarming rate. We chose not to use higher doses because of the risk of severe hypotension associated with their use.[24 25] In the present study, the mean arterial blood pressure was significantly lower in the amrinone group than in the control group at the start of rewarming, although no patient in either group required treatment for hypotension. However, the possibility of hypotension due to amrinone, especially in patients who demonstrate cardiovascular instability before anaesthesia, should be considered.

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References

1 Baker KZ, Young WL, Stone JG, Kader A, Baker CJ, Solomon RA. Deliberate mild intraoperative hypothermia for craniotomy. *Anesthesiology* 1994; **81**: 361–7.

2 Sessler DI. Deliberate mild hypothermia. *J Neurosurg Anesthesiol* 1995; **1**: 38–46.

3 Hindman BJ, Todd MM, Gelb AW, *et al.* Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. *Neurosurgery* 1999: **44**; 23–32

4 Kawaguchi M, Inoue S, Sakamoto T, Kawaraguchi Y, Furuya H, Sakaki T. The effects of prostaglandin E1 on intraoperative temperature changes and the incidence of postoperative shivering during deliberate mild hypothermia for neurosurgical procedures. *Anesth Analg* 1999; **88**: 446–51

5 Theard MA, Tempelhoff R, Crowder CM, Cheng MA, Todorov A, Dacey RG Jr. Convection versus conduction cooling for induction of mild hypothermia during neurovascular procedures in adults. *J Neurosurg Anesthesiol* 1997; **9**: 250–5.

6 Baker KZ, Stone JG, Jackson L, *et al.* Intraoperative nitroprusside does not speed rewarming from mild hypothermia. *J Neurosurg Anesthesiol* 1995; **7**: 316.

7 Kurz A, Sessler DI, Birnbauer F, *et al.* Thermoregulatory vasoconstriction impairs active core cooling. *Anesthesiology* 1995; **82**: 870–6

8 Greene PS, Cameron DE, Mohlala ML, Dinatale JM, Gardner TJ. Systolic and diastolic left ventricular dysfunction due to mild hypothermia. *Circulation* 1989; **80**: III44–8

9 Meisheri KD, Palmer RF, Van-Breemen C. The effect of amrinone on contractility, Ca^{2+} uptake and cAMP in smooth muscle. *Eur J Pharmacol* 1980; **61**: 159–65

10 Yoshida K, Watanabe H, Nakamura S. Intraarterial injection of amrinone for vasospasm induced by subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 1997; **18**: 492–6

11 Sessler DI, McGuyre J, Moayeri A, Hynson J. Isoflurane-induced

vasodilation minimally increases cutaneous heat loss. *Anesthesiology* 1991; **74**: 226–32

12 Matsukawa T, Sessler DI, Sessler AM, *et al.* Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 1995; **82**: 662–73

13 Hynson J, Sessler DI. Intraoperative warming therapies: a comparison of three devices. *J Clin Anesth* 1992; **4**: 194–9

14 Belani K, Sessler DI, Sessler AM, *et al.* Leg heat content continues to decrease during the core temperature plateau in humans anesthetized with isoflurane. *Anesthesiology* 1995; **82**: 662–73

15 Stoen R, Sessler DI. The thermoregulatory threshold is inversely proportional to isoflurane concentration. *Anesthesiology* 1990; **72**: 822–7

16 Shitara T, Wajima Z, Ogawa R. Dobutamine infusion modifies thermoregulation during general anesthesia. *Anesth Analg* 1996; **83**: 1154–9

17 Clough D, Kurz A, Sessler DI, Christensen R, Xiong J. Thermoregulatory vasoconstriction does not impede core warming during cutaneous heating. *Anesthesiology* 1996; **85**: 281–8

18 Little DM. Hypothermia. *Anesthesiology* 1959; **20**: 842–77

19 Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F. The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than young patients. *Anesthesiology* 1993; **79**: 465–9

20 Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T. Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decrease heat loss. *Anesthesiology* 1992; **76**: 670–5

21 Sessler DI, Olofsson CI, Rubinstein EH. The thermoregulatory threshold in humans during nitrous oxide–fentanyl anesthesia. *Anesthesiology* 1988; **69**: 357–64

22 Xiong J, Kurz A, Sessler DI, *et al.* Isoflurane produces marked and nonlinear decreases in the vasoconstriction and shivering thresholds. *Anesthesiology* 1996; **85**: 240–5

23 Washington DE, Sessler DI, McGuire J, Hynson J, Schroeder M, Moayeri A. Painful stimulation minimally increases the thermoregulatory threshold for vasoconstriction during enflurane anesthesia in humans. *Anesthesiology* 1992; **77**: 286–90

24 Berner M, Jaccard C, Oberhansli I, Rouge JC, Friedli B. Hemodynamic effects of amrinone in children after cardiac surgery. *Intensive Care Med* 1990; **16**: 85–8

25 Shibata T, Suehiro S, Minamimura H, *et al.* Hemodynamic effects of amrinone, phosphodiesterase inhibitor, early after coronary artery bypass grafting. *Nippon Kyobu Geka Gakkai Zasshi* 1996; **44**: 2027–31

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Autologous blood transfusion in total knee replacement surgery

D. Thomas[1]*, K. Wareham[1], D. Cohen[2] and H. Hutchings[1]

[1]*Morriston Hospital, Swansea NHS Trust, Swansea SA6 6NL, UK.* [2]*University of Glamorgan, Pontypridd CF37 1DL, UK*

**Corresponding author*

We compared allogeneic blood usage for two groups of patients undergoing total knee replacement surgery (TKR). Patients were randomized to receive either their post-operative wound drainage as an autotransfusion (n=115) after processing or to have this wound drainage discarded (n=116). Allogeneic blood was transfused in patients of either group whose haemoglobin fell below 9 g dl^{-1}. Only 7% of patients in the autotransfusion group required an allogeneic transfusion compared with 28% in the control group (P<0.001). There was no hospital mortality and only 3% mortality from all causes at the study completion, which spanned 6 months to 3 yr. There was a higher incidence of infection requiring intervention in the allogeneic group (P<0.036). Total patient costs were £113 greater in the autotransfusion group. We conclude that in this type of surgery post-operative cell salvage is a safe and effective method for reducing allogeneic blood use.

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The identification of transfusion transmitted diseases' such as Human Immunodeficiency Viruses (HIV), Hepatitis C (Hep C) and new variant Creutzfeldt-Jakob (nvCJD) disease has led to an increasing number of tests which need to be performed before allogeneic blood transfusion. The current allogeneic blood supply is probably the safest ever produced. However, this statement does not take account of the evolution and subsequent identification of other illnesses, which may be transmitted by blood transfusion. The most recent problem relates to the transmission via blood transfusion of the prion thought to cause vCJD. This has led to the leucodepletion of all blood products within the UK. The increased cost of blood products has added considerable enthusiasm in medical circles to decrease their use, and subsequent patient exposure to allogeneic blood.

There is some inconclusive evidence,[1] suggesting that patients may suffer fewer peri-operative infections if they avoid allogeneic blood transfusion at the time of surgery. Using autotransfusion may be one way of maintaining peri-operative haemoglobin concentrations, reducing the need for allogeneic blood transfusion.[2–5] If peri-operative transfusion practices were aimed at a 'minimum' haemoglobin concentration, rather than trying to maintain a pre-operative value, this would further decrease peri-operative transfusions.

Because of the paucity of evidence in the literature from randomized, controlled studies we decided to undertake a randomized controlled trial to confirm our findings from a small pilot study,[6] which suggested that a marked reduction in allogeneic blood transfusion could be achieved safely by using post-operative red cell salvage (PRCS) and a haemoglobin 'transfusion trigger'.

Patients and methods

This was a single-centre, randomized controlled study of patients undergoing TKR. After review and approval by the Local Research Ethics Committee, we obtained informed consent and studied 231 patients. Patients were allocated randomly to one of two treatment groups; one group received allogeneic blood (if their haemoglobin fell below a pre-set transfusion trigger of 9 g dl^{-1}) and the other group received autotransfusion of wound drainage if the volume was greater than 125 ml post-operatively.

The collected blood was washed and re-suspended in saline before re-infusion using a centrifugal cell washing machine (Cell Saver 5 Haemonetics). The patients in the cell salvage group were also transfused if their haemoglobin fell below the preset trigger after autotransfusion. We chose a transfusion trigger to standardize the transfusion incidence in both groups. Although the American Society of Anaesthesiology recommended a trigger of 7 g dl^{-1}, we felt this was perhaps too aggressive and it would be difficult to apply. Many anaesthetists would be reluctant to withhold blood at this level of anaemia knowing the correlation with an optimum oxygen delivery and haemoglobin of 10 g dl^{-1}.

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Table 1 Patient characteristics. *Fischer's exact test, † Independent samples *t*-test

Description	Autologous (cell salvage) Females n=71	Males n=44	Allogenic (homologous) Females n=61	Males n=55	P-value 0.18*
Mean age (range)	70.5 (32–95) yr	67.4 (38–85) yr	70.2 (40–87) yr	69.7 (48–88) yr	0.59†
Mean ASA grade (range)	2.1 (1–3)	2.0 (1–3)	2.1 (1–3)	1.9 (1–3)	0.56†
Smokers	9	10	6	9	0.35*
Previous transfusion	15	9	17	12	0.09*
Asprin/NSAIDs use	25	19	24	31	0.16*

Haemoglobin concentrations were measured on days 1, 2, 3, 4, and 7 in all patients. The TKR was conducted as routine. Data were collected by research nurses for post-operative length of stay, peri-operative and post-hospital discharge infection rates, adverse events, wound healing rates and quality of life (EuroQol EQ-5D).[7]

One of the investigators scrutinized all adverse events in a blinded fashion to determine which were possibly related to transfusion effects, for example, wound infection, embolic events, myocardial ischaemic events, and cardiopulmonary complications.

Data were loaded onto an SPSS version 7.5 computer programme (SPSS Inc., Chicago, USA) and all statistical analysis was performed using this program. The level of statistical significance for all tests was set up at a P-value of <0.05. For bivariate analysis, a two-tailed test of significance was used. Patient characteristics were examined using Fischer's Exact Test or the Independent Sample t-test. In respect to adverse events, the comparison was examined using chi-squared test.

Results

Of the 231 patients, 98 were males and 115 were randomized into the cell salvage group. Characteristics of patients in the two groups were comparable (Table 1). Although anaesthetic technique was not standardized, Table 2 depicts the type of anaesthesia used and the similarity between the groups. The majority of patients received a Johnson and Johnson prosthesis (75 in the autologous arm and 77 in the allogeneic arm) with the remaining patients in both groups having a De Puy prosthesis. All knee replacements were performed under tourniquet, with the pressure set according to systolic arterial pressure. Patients in both groups were transfused with allogeneic blood if their haemoglobin concentration fell below the preset trigger of 9 g dl^{-1}.

The study was analysed on an intention to treat basis. Of the 115 patients randomized into the autologous arm of the study, 85% received an autologous transfusion. The remaining 18 patients were not transfused because of lack of staff to operate the cell salvage equipment (13 patients), insufficient blood collection (four patients), and tourniquet failure (one patient).

Twelve patients in the autologous arm of the study received an allogeneic transfusion. Two were inappropriate,

Table 2 Methods of anaesthesia

Description	Group 1	Group 2
General alone	67	67
General+femoral block	24	23
General+spinal block	6	9
General+epidural	7	7
Spinal alone	7	6
Epidural alone	0	1
Femoral alone	3	3
Spinal+epidural	1	0

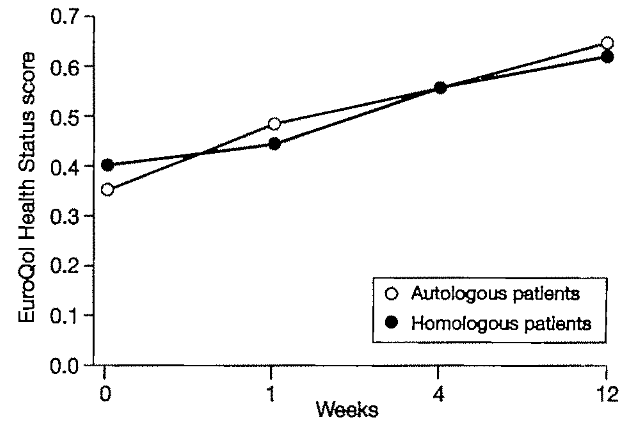

Fig 1 EuroQol health status score.

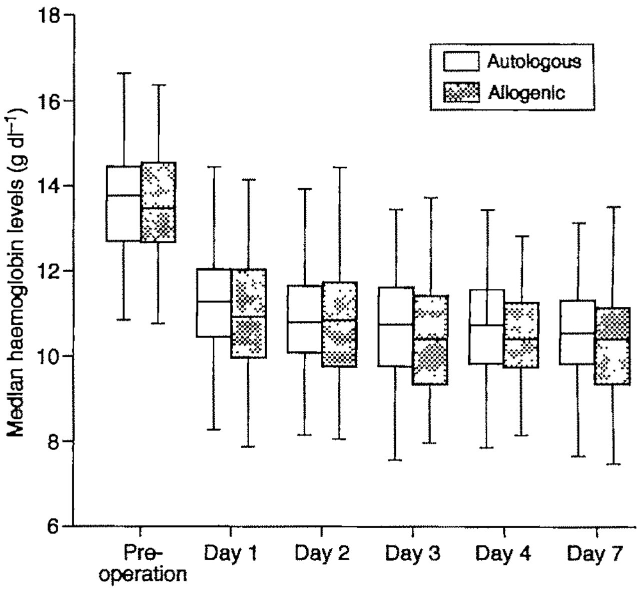

Fig 2 Median haemoglobin concentrations. No significant differences.

Table 3 Readmission by group: conditions considered possibly related to blood products

Males/females (Autologous group)		**Males/females (Allogeneic group)**	
Age/sex	**Problem**	**Age/sex**	**Problem**
83 F	Recurrent pulmonary embolism/ wound abscess: died	72 M	Cellulitis – ?DVT – doppler nad
66 M	Wound infection	65 F	DVT
72 F	Wound infection persisted: sinus explored which did not connect to knee replacement	70 M	Infected wound
		88 M	Cellulitis
		70 F	Wound infection
		65 M	Acute anaemia: 4 units blood transfused
		78 F	Superficial wound infection: antibiotics commenced
		60 M	? PE – heparinized overnight
		68 M	Wound infection

Table 4 Average per patient costs (£, 1998) of allogeneic and autologous blood transfusion

Description	**Cost of allogeneic transfusion (£)**	**Cost of autologous transfusion (£)**
Allogeneic blood	27.96	12.20
Staff time		49.34
Capital and servicing		24.12
Disposables	00.74	80.12
Total direct cost	28.70	165.78
Readmission	34.65	11.66
GP consultation	01.55	00.72
Total indirect costs	36.20	12.38
Total per patient cost	64.90	178.16

as both patients had a haemoglobin concentration greater than 9 g dl^{-1} and were asymptomatic, and could be classed as a procedure deviation. The remaining 10 patients had haemoglobin concentrations between 7.6 and 8.9 g dl^{-1}. Of the 10 patients whose transfusion was warranted, four of these were from the 18 patients in whom cell salvage failed and a further three patients had only a small amount of blood salvaged (<150 ml).

In the control group, 33 patients received allogeneic blood. The majority (76%) received two units, 6% three units, 6% four units, and 12% one unit.

There was no significant difference in length of stay, wound healing, serious adverse events or mortality, or health related quality of life (EuroQol) 6 months after surgery (Fig. 1). There was a significantly lower (7%) incidence of allogeneic blood transfusion in the cell salvage group, compared with 28% in the controls ($P<0.001$). There was no difference in post-operative mean haemoglobin concentration between the two groups (Fig. 2).

In relation to transfusion practice, we found significantly fewer re-admissions to hospital ($P<0.008$) and visits to general practitioners ($P<0.043$) in patients in the autologous blood transfusion group (Table 3). Infective complications were increased in allogeneic recipients ($P=0.036$), with increasing significance ($P=0.025$) if all patients receiving allogeneic blood were placed in the allogeneic group.

A comparison of the cost difference between allogeneic transfusion and autologous transfusion was made by one of the authors (DC). A summary of the findings is shown (Table 4).

Discussion

This current study showed that a decrease in allogeneic blood use could be achieved by using PRCS. In a previous study,[6] we showed that the use of PRCS could dramatically reduce patients' exposure to allogeneic blood (from 82 to 18%), without clinical detriment, as all patients left hospital. In that study, as with this one, there was no statistical difference in the discharge haemoglobin concentrations. The design of our original pilot study did not apply a strict transfusion trigger to both groups; we were trying to show how the use of PRCS could improve transfusion practice over routine clinical practice. However, in this study we have assessed the difference in transfusion of allogeneic blood between the two groups whilst applying a strict transfusion trigger to both randomized groups. There is no doubt that by applying rational transfusion principles, a large decrease in allogeneic transfusion can be achieved without the use of any autologous transfusion methods.

The present study shows that further significant reductions can be achieved by the use of PRCS, decreasing overall use of allogeneic transfusion to below 7% in the autologous group. Despite publication of other studies showing a similar trend,[2–6 8] our study is one of the largest randomized controlled trials yet performed. Criticism has also been levelled at the lack of outcome measures applied to many studies assessing the practice of PRCS. In our study, no patients failed to leave hospital from either group. It was reassuring that the end of study mortality (in some cases indicating a 2-yr follow up and/or a minimum of 6 months post-hospital discharge) was similar in both groups, when deaths from all causes were considered. This mortality rate compared very favourably with a large orthopaedic audit reported from the Mayo clinic.[9]

The data did not support a difference in immediate post-operative infection or earlier hospital discharge, as had been suggested by earlier publications. The well-recognized effect of immunomodulation because of allogeneic blood transfusion was not apparent. This may add weight to the argument that universal leucodepletion offers only minor benefit. The length of stay was consistent with data from other Welsh hospitals (personal communication, Department of Public Health). Assessment using EuroQol Health State score did not show a difference between groups (Fig. 1), in contrast to the proposal that patients receiving autologous blood have improved health and well being when compared with those receiving allogeneic blood. It was noted that the EuroQol scores improved in both groups when pre-operative and 12 weeks post-operative scores were compared.

The only area where we found a statistical difference between groups was in the post-hospital infective complications with allogeneic recipients having increased infection. This effect became even more significant if those who received rescue transfusion were included in the allogeneic group. These findings are supported by the reduced readmissions and visits to general practitioners by patients who had been randomized to receive an autologous transfusion.

We have shown that reducing allogeneic transfusion can be achieved safely by using a combination of PRCS and limiting the transfusion when the patient has haemoglobin greater than 9 g/dl^{-1}. This may be considered as a conservative haemoglobin trigger and appropriate for even those patients with significant cardiac disease.[10–15] Of course the group of patients undergoing this type of joint replacement are more elderly than the general population and thus more likely to suffer from heart disease. We believe therefore that such blood conservation techniques are clinically indicated in the light of present evidence. There is a need to seek safe alternatives to allogeneic blood, both to decrease the risk of future unknown blood-borne transmitted disease and to increase the availability of allogeneic blood supplies where there are no available alternatives.

Our cost analysis showed that autologous transfusion was overall more expensive, despite having lower re-admission and post-operative general practitioner costs. At the time of the study the unit cost of allogeneic blood was £50.83. In addition, staff time of £49.34 was estimated on a cell-salvage operator being present throughout the post-operative collection period. In practice, this is not necessary. Processing of the drained blood had a mean time of 20 min. These two factors would now make a cost comparison more favourable.

Moreover, although autologous transfusion was not shown to be cost-effective, it should be noted that this analysis was short term and ignores the value attached to reduced risk of transmission of virus related illness. A recent US study[16] has estimated median willingness to pay for autologous blood to reduce this risk at $900 per patient, which is considerably more than the excess cost per patient in the experimental arm of the present study. It seems that the reluctance to adopt such techniques in routine practice is because of a number of factors. This includes cost, organization and, perhaps, motivation. The recent increase in cost of production of all red cell products, because of improved testing for Hep C and the leucodepletion of all blood products to decrease the risk of nvCJD transmission, may make post-operative red cell salvage more attractive.

We would hope that if cost is the most important driver, then significant reduction in red cell use, without increased morbidity or mortality, might aid motivation and organization of such transfusion alternatives.

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References

1 Murphy P, Heal JM, Blumberg N. Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusion. *Transfusion* 1991; **31**: 212–7

2 Heddle NM, Brox WT, Klama LN, Dickson LL, Levine MN. A randomised trial on the efficacy of an autologous blood drainage and transfusion device in patients undergoing elective knee arthroplasty. *Transfusion* 1992; **32**: 742–6

3 Clements DH, Thomas MD, Sculco P, *et al.* Salvage and reinfusion of postoperative sanguineous wound drainage. *J Bone Joint Surg* 1992; **74**: 646–51

4 Goulet JA, Arbor A, Michigan TJ, *et al.* Intraoperative autologous transfusion in Orthopaedic patients. *J Bone Joint Surg* 1989; **71**: 3–8

5 Lisander B, Ivarsson I, Jacobsson SA. Intraoperative autotransfusion is associated with modest reduction of allogeneic transfusion in prosthetic hip surgery, *Acta Anaesthesiol Scand* 1998; **42**: 707–12

6 Shenoliker A, Wareham K, Newington D, Thomas D, Hughes J, Downes M. Cell salvage auto transfusion in total knee replacement surgery. *Trans Med* 1997; **7**: 277–80

7 EuroQol Group. EuroQol. A new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208

8 Newman JH, Bowers M, Murphy J. The clinical advantages of autologous transfusion. *J Bone Joint Surg* 1997; **79**: 630–2

9 Warner DO, Warner DR, Schroeder KP, *et al.* Changing transfusion practices in hip and knee arthroplasty. *Transfusion* 1998; **38**: 738–44

10 Wahr J. Risk of under transfusion, Thematic Reports, 1st Annual Meeting Network for advancement of transfusion alternatives. January 31 to February 1, 2000

11 Carson JL, Duff A, Berlin JA, *et al.* Perioperative blood transfusion and postoperative mortality. *JAMA* 1998; **279**: 199–205

12 Spahn DR, Zollinger A, Schlumpf RB, *et al.* Hemodilution tolerance in elderly patients without known cardiac disease. *Anaesth Analg* 1996; **82**: 681–6

13 Goodnough LT, Shafron D, Marcus RE. The impact of preoperative autologous blood donation on orthopaedic surgical practice. *Vox Sang* 1990; **59**: 65–9

14 Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anaemia and cardiac morbidity in high-risk

vascular patients in the intensive care unit. *Critical Care Med* 1993; **21**: 860–6

15 Czer LS, Shoemaker WC. Optimal haematocrit value in critically ill postoperative patients. *Surg Gynaecol Obstet* 1978; **147**: 363–8

16 Lee LS, Neumann P, Hallowell C, Cannon M, Weinstein M, Johannesson M. Patients willingness to pay for autologous blood donation. *Health Policy* 1997; **40**: 1–12

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Double-blind comparison of ropivacaine 7.5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for sciatic nerve block

C. Connolly, D. M. Coventry* and J. A. W. Wildsmith

Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
**Corresponding author*

Two groups of 12 patients had a sciatic nerve block performed with 20 ml of either ropivacaine 7.5 mg ml^{-1} or bupivacaine 5 mg ml^{-1}. There was no statistically significant difference in the mean time to onset of complete anaesthesia of the foot or to first request for post-operative analgesia. The quality of the block was the same in each group. Although there was no statistically significant difference in the mean time to peak plasma concentrations the mean peak concentration of ropivacaine was significantly higher than that of bupivacaine. There were no signs of systemic local anaesthetic toxicity in any patient in either group.

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Keywords: anaesthetic techniques, regional, sciatic; anaesthetics local, ropivacaine; anaesthetics local, bupivacaine; pharmacokinetics, bupivacaine

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Sciatic nerve block is a useful anaesthetic technique for unilateral lower limb surgery, particularly in patients thought unsuitable for a central block. A long acting local anaesthetic agent will provide prolonged post-operative analgesia, and bupivacaine has been considered the drug of choice for this reason. However, concerns have been raised over its potential cardiotoxicity after inadvertant i.v. administration. Ropivacaine, a newer amide agent, appears to have similar clinical characteristics, but less potential for systemic toxicity.[1–4] Although a significant mass of local anaesthetic is required for sciatic nerve block, there have been few reports of systemic drug disposition. This study was designed to compare both the clinical efficacy and pharmacokinetics of sciatic nerve block with either ropivacaine 7.5 mg ml^{-1} or bupivacaine 5 mg ml^{-1}.

Patients and methods

Twenty-four ASA 1–3 patients presenting for elective unilateral metatarsal osteotomy under sciatic nerve block gave informed consent for the study, which was approved by the local ethics committee. Each patient received temazepam 10–20 mg orally, 1–2 h before surgery. Before the sciatic nerve block, each patient was allocated randomly to one of two groups: group A received 20 ml ropivacaine 7.5 mg ml^{-1}, and group B 20 ml bupivacaine 5 mg ml^{-1}.

On arrival in the anaesthetic room, a 20 g cannula was placed in a peripheral vein for the administration of sedative and other drugs, and a 14 g cannula was inserted in a vein of the antecubital fossa of the other arm for blood sampling. In addition to routine clinical monitoring devices, a separate temperature probe (Hewlett Packard – M1029A) was applied to the dorsum of each foot, over the space between the first and second metatarsal bones. These were covered and insulated with gauze swabs and the skin temperature of both feet was measured continuously, and recorded every minute.

Midazolam 1–2 mg was administered i.v. before the block procedure, which was performed aseptically. After infiltration of the skin and subcutaneous tissues with 1% lidocaine, the sciatic nerve injection was performed using the posterior approach of Labat. All blocks were performed by the same investigator, and neither patient or block administrator knew which solution was used. The nerve was located using a 120 mm, 21 swg, short-bevelled insulated needle attached to a 'Stimuplex' peripheral nerve stimulator (B. Braun medical). Needle placement was considered optimal when maximal gastrocnemius contraction and plantar flexion of the foot was obtained at a current of 0.5 mA. After careful aspiration, the test solution was injected over a 2-min period. The end of the injection was defined as time zero.

Development of nerve block was assessed in three ways. The sensory response to pin-prick on the dorsal and plantar aspects of the foot was assessed using a short-bevelled 27 swg dental needle before, and 5, 10, 15, 20, 25, and 30 min after injection. Sensation was categorized as 'sharp' (same as the contra-lateral foot), 'dull' (pin-prick perceived

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as pressure), or 'absent' (complete loss of awareness of pinprick). Onset of block was defined as the time taken to achieve complete loss of sensation on both dorsal and plantar aspects of the foot.

Motor block was assessed using a simple 3 point score:

0=normal muscle power;
1=reduced power (plantar or dorsiflexion); and
2=complete motor block (plantar and dorsiflexion).

The time of onset of a progressive increase in the temperature of the 'blocked' foot was used to indicate the onset of sympathetic nerve block.

Once the sensory block was complete, an arterial tourniquet was applied to the calf, one hand's breadth below the tibial tuberosity to avoid proximal compression of the peroneal nerve. The patient was then taken into the operating theatre and positioned for surgery. The foot was exanguinated using an Esmarch bandage, and the arterial tourniquet inflated. During the surgical procedure the patient listened to music by themselves through headphones and was able to communicate with an investigator at all times.

The clinical efficacy of the block was assessed in two ways. Patients were asked to provide a verbal rating of the quality (excellent, good, fair, poor) of anaesthesia 10 min after the start of surgery, and again immediately after its end. The time that elapsed until the patient first requested post-operative analgesia was recorded as an indicator of the duration of sensory block.

Peripheral venous blood samples were taken before, and 10, 20, 30, 45, 60, and 120 min after the end of the injection. The blood was centrifuged immediately and the supernatant plasma frozen at -20°C for subsequent batch analysis using a gas chromatographic technique with a coefficient of variation of 6%.

Data are presented as median (range) and statistical comparisons were performed using the Mann–Whitney *U* test for the characteristics of the nerve block. Peak concentrations (C_{max}) of the two drugs were compared by *t*-test after log transformation, and times to peak concentration (T_{max}) by Wilcoxon signed rank test.

Results

More females than males were recruited to the study, but there were no differences in patient characteristics between the two groups (Table 1). All patients underwent a first metatarsal osteotomy, with a silastic implant or joint fusion. No patient required supplementation of the sciatic nerve block to allow the surgery to commence, but one needed a saphenous nerve block (10 ml prilocaine 10 mg ml^{-1}) 5 min before the end of the operation to allow medial proximal extension of the wound.

All patients received i.v. midazolam. The dose was titrated to individual patient requirements, but all patients were awake and responsive. The median and range for total dose of midazolam throughout the whole procedure was 2 (range 0–6) mg.

Table 1 Patient characteristics expressed as mean (SD)

	Group A (ropivacaine)	Group B (bupivacaine)
Age (yr)	62.3 (7.3)	57.9 (13.4)
Female	10	9
Male	2	3
Weight (kg)	75.4 (16.7)	64.3 (11.6)

Table 2 Clinical characteristics of blocks expressed as median (range)

	Ropivacaine	Bupivacaine	*P*
Time to onset of temperature increase (min)	5 (4–15)	5 (5–23)	0.73
Time to onset of complete anaesthesia (min)	27.5 (5–40)	25 (5–35)	0.81
Duration of analgesia (h)	13.4 (8.6–17.8)	15.8 (9.1–19.7)	0.28

There was some variability in the time to the onset of both a sustained increase in skin temperature and complete anaesthesia of the foot, but there were no differences between the two groups (Table 2). Eight patients in the ropivacaine, and seven in the bupivacaine group, developed complete motor block of the foot. The remaining patients developed only some degree of motor weakness, but this did not interfere with surgery. Ten min after surgery began, 10 patients in the ropivacaine group rated anaesthesia as 'excellent' and two as 'good'. In the bupivacaine group, 10 rated anaesthesia as 'excellent' and two as 'fair'.

At the end of surgery, 11 patients in each group rated anaesthesia as 'excellent' and one in each group as 'good'. Both drugs produced prolonged analgesia, with the time to first request for analgesia being slightly longer with bupivacaine. This difference was not statistically significant (Table 2).

Mean peak plasma concentration of ropivacaine was significantly higher than that of bupivacaine, but in no patient did the maximum figure exceed the accepted threshold for systemic effects (Table 3). The time taken to reach the peak plasma concentration was the same in both groups.

Discussion

This study has shown that 20 ml of either ropivacaine 7.5 mg ml^{-1} or bupivacaine 5.0 mg ml^{-1} produces effective sciatic nerve block after nerve stimulator guided injection, although it is arguable that it might have been more logical to compare equal concentrations of the two drugs. However, these are the concentrations of these two drugs that are licensed in the UK for major peripheral nerve block and it was thought useful to compare the two preparations. A reduction in the volume of ropivacaine 7.5 mg ml^{-1} would

Table 3 Pharmacokinetic data expressed as mean (SD)

	Ropivacaine	Bupivacaine	P
C_{max} (mg litre^{-1})	1.1 (0.5)	0.6 (0.3)	0.002
Highest individual C_{max} (mg litre^{-1})	1.8	1.1	N/a
T_{max} (min)	45.8 (27.0)	35.0 (14.9)	0.352

have allowed comparison of equal doses of the two drugs, but with differing volumes. Because 20 ml of each solution was used, the dose discrepancy produced in comparing the two licensed preparations is acknowledged, although equal dose comparisons of these two drugs using other major peripheral nerve injection techniques (brachial plexus block) have shown little difference between them.[5–8] Supplementation of the sciatic nerve block with saphenous block was required in only one patient, when the surgical wound required proximal extension. This correlates well with a previous study,[16] in which 5% of patients required supplementation of sciatic block with saphenous nerve block.

Although similar doses of local anaesthetic are required, there has been far less study of systemic drug disposition after sciatic than epidural block. The peak plasma concentrations reported here for bupivacaine are of the same order as seen previously. Coventry and Todd compared standard and alkalinized formulations of bupivacaine with epinephrine in a slightly greater dose (2 mg kg^{-1}) than used here.[10] Peak plasma concentrations, 0.4 and 0.6 mg litre^{-1}, respectively, were somewhat lower than reported here, but epinephrine was not added in the present study. Others have studied combinations of lower limb nerve blocks with bupivacaine. Moore and colleagues observed a peak plasma concentration of 1.6 mg litre^{-1} after 400 mg bupivacaine with epinephrine for combined sciatic, femoral, and lateral cutaneous nerve of thigh block.[11] Misra and colleagues compared plasma concentrations after bupivacaine 3 mg kg^{-1}, plain or with epinephrine, after combined sciatic and femoral 3-in-1 block, and noted peak concentrations of 0.75 and 0.7 mg litre^{-1}, respectively.[12]

The peak concentrations of ropivacaine were somewhat higher than those for bupivacaine (Table 3). Primarily this would reflect the greater dose administered, although slightly higher concentrations of ropivacaine have been reported than after injection of equal doses of bupivacaine epidurally.[13] Lee and colleagues did report that the threshold for early signs of systemic toxicity with ropivacaine was in the range 1–2 mg litre^{-1}, but that study involved direct i.v. infusion of the drug in volunteers.[14] Many subsequent clinical studies have found plasma concentrations of ropivacaine to be in that range, but, as here, this has been without any indication of systemic toxicity.[13] Much higher concentrations have been reported after accidental i.v. administration of ropivacaine, but again without any real concern for patient safety.[15]

This study was designed to assess also the clinical efficacy of sciatic nerve block as the primary anaesthetic for foot surgery and to compare the effects of the two commercially available long acting agents, both of which performed well. Sciatic block is a useful technique for unilateral lower limb surgery, having several advantages over central nerve block in elderly patients in whom a regional technique is preferred. This is especially so in terms of avoidance of the complications to which the elderly are particularly disposed such as hypotension and urinary retention. It may also be used more readily in the presence of a minor degree of coagulopathy or after head injury when central block is relatively contraindicated. The more selective block distribution may improve post-operative mobility, and longer acting agents provide prolonged post-operative analgesia.

Adverse effects of sciatic block are rare, but would include intravascular injection.[9] Because a significant total dose of local anaesthetic is deposited at a very specific site to achieve accurate block, it is possible that a significant proportion of the total dose could be injected i.v. The length of needle used may also conceal intravascular placement particularly if over-vigorous aspiration is applied. The total dose should, therefore, be given slowly in increments and the reduction in cardiotoxicity afforded by ropivacaine should be seen as a significant advantage in these circumstances. The addition of epinephrine to either of the study agents does not appear to offer any clinical advantage in terms of duration of block, but may be useful in determining early intravascular placement.

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References

1 Feldman HS, ArthurGR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. *Anesth Analg* 1989; **69**: 794–801

2 Nancarrow C, Rutten AJ, Runciman WG, *et al.* Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine and ropivacaine in sheep. *Anesth Analg* 1989; **69**: 276–83

3 Scott DB, Lee A, Fagan D, *et al.* Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

4 McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76**: 300–7

5 Hickey R, Blanchard J, Hoffman J, Sjovall J, Ramamurthy S. Plasma concentrations of ropivacaine given with or without epinephrine for brachial plexus block. *Can J Anaesth* 1990; **37**: 878–82

6 Hickey R, Candido KD, Ramamurthy S, *et al.* Brachial plexus block with a new local anaesthetic: 0.5% ropivacaine. *Can J Anaesth* 1990; **37**: 732–8

7 Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. *Anesthesiology* 1991; **74**: 639–42

8 Hickey R, Rowley CL, Candido KD, Hoffman J, Ramamurthy S, Winnie AP. A comparitive study of 0.25% ropivacaine and 0.25% bupivacaine for brachial plexus block. *Anesth Analg* 1992; **75**: 602–6

9 Coventry DM. Plasma bupivacaine concentration after inadvertant intravenous injection. *Anaesthesia* 1989; **44**: 162

10 Coventry DM, Todd JG. Alkalinisation of bupivacaine for sciatic nerve blockade. *Anaesthesia* 1989; **44**: 467–70

11 Moore D, Mather L, Bridenbaugh L, Balfour R, Lysons D, Horton W. Arterial and venous plasma levels of bupivacaine following peripheral nerve block. *Anesth Analg* 1976; **55**: 763–8

12 Misra U, Pridie A, McClymont C, Bower S. Plasma concentration of bupivacaine following combined sciatic and femoral 3-in-1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; **66**: 310–3

13 Tucker GT. Ropivacaine: human pharmacokinetics. *Am J Anesthesiology* 1996; **24**: 8–13

14 Lee A, Fagan D, Lamont M, *et al.* Disposition kinetics of ropivacaine in humans. *Anaesth Analg* 1989; **69**: 736–8

15 Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *Br J Anaesth* 1991; **66**: 31–7

16 Kilpatrick AWA, Coventry DM, Todd JG. A comparison of two approaches to sciatic nerve block. *Anaesthesia* 1992; **47**: 155–7

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Rocuronium: high risk for anaphylaxis?

M. Rose[1] **and M. Fisher**[1 2*]

[1]*Royal North Shore Hospital of Sydney, St Leonards, NSW, Australia.* [2]*Department of Anaesthesia, University of Sydney, Sydney, Australia*

**Corresponding author: Intensive Therapy Unit, Royal North Shore Hospital, Pacific Highway, St Leonards, NSW 2065, Australia*

Patients suspected of anaphylaxis during anaesthesia have been referred to the senior author's clinic since 1974 for investigation. Since release of rocuronium on to the worldwide market, concern has been expressed about its propensity to cause anaphylaxis. We identified 24 patients who met clinical and laboratory (intradermal, mast cell tryptase and morphine radioimmunoassay) criteria for anaphylaxis to rocuronium. The incidence of rocuronium allergy in New South Wales, Australia has risen in parallel with sales, while there has been an associated fall in reactions to other neuromuscular blocking drugs. Data from intradermal testing suggested that rocuronium is intermediate in its propensity to cause allergy in known relaxant reactors compared with low-risk agents (e.g. pancuronium, vecuronium) and higher-risk agents (e.g. alcuronium, succinylcholine).

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Anaphylaxis during anaesthesia is a significant contributor to morbidity and mortality during the perioperative period. It has been estimated to be of the order of 1:980 to 1:20 000 by the Boston Collaborative Drug Surveillance Survey,[1] but published international figures vary within this range.

Rare adverse effects of drugs, such as anaphylaxis, do not usually become apparent until the drug is established in clinical usage. It may be misrepresented (higher or lower) by small numbers of reactors until the drug has been observed extensively after release on to the market. In addition, estimation of prevalence requires knowledge of both numbers of reactors and total numbers of doses given in the population. Estimation of the number of reactors is hampered by difficulty in definitive diagnosis and referral of reactors, while the number of doses of a drug given is at best an estimate from drug sales data.

Another method of assessing the relative likelihood of a new neuromuscular blocking drug (NMBD) to cause anaphylaxis is to determine cutaneous sensitivity in a population of patients known to be relaxant reactors.[2]

Rocuronium was introduced in Australia in 1996. It is a monoquaternary NMBD that shares its aminosteroid structure with pancuronium and vecuronium, which are less likely to produce anaphylaxis than other NMBDs.[2 3] In addition, rocuronium causes less direct histamine release than the benzylisoquinolinium-derived NMBDs, such as atracurium and mivacurium.[4] An early French study[5] of cutaneous sensitivity in NMBD reactors suggested that rocuronium may be more likely to cause anaphylaxis than the other aminosteroid drugs. Subsequently, three anaphylactic reactions were reported in 2000 uses in the UK.[6] Concern has been expressed in Australia regarding an apparently high number of anaphylactic reactions to rocuronium.

Methods and patient selection

Patients were referred to the senior author's clinic after having being suspected of anaphylaxis during anaesthesia.

Criteria for anaphylaxis

Patients were suspected to have had an anaphylactic event when the condition was life-threatening and involved two or more of the classic signs of anaphylaxis: hypotension, bronchospasm, dermatological signs (erythema, rash or urticaria) and angio-oedema. The diagnosis was regarded as confirmed if results of intradermal testing, radioimmunoassay (RIA) or mast cell tryptase (MCT) testing were positive.[7] Mast cell tryptase is the single most useful test to confirm an anaphylactic event,[8–10] whereas the most valuable test to determine the identity of the responsible agent is intradermal testing. RIA testing can also help to identify a responsible agent, especially when intradermal tests are negative.[8] Patients whose reactions were severe and clinically likely to be anaphylaxis but whose reactions

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involved a single organ system were admitted to the database only if there was supporting laboratory evidence.

Testing

Intradermal testing,[8 11] MCT testing[12] and morphine RIA testing for IgE antibodies to NMBDs[13] were performed according to published protocols.

Intradermal testing was performed 4–6 weeks after the reaction using appropriate dilutions of drugs that have been found to be unlikely to produce local false-positive reactions as a result of direct histamine release. Concentrations of the drugs used are presented in Table 1. The skin was lightly cleaned with isopropyl alcohol, the skin beneath the test site also being cleaned with isopropyl alcohol to exclude sensitivity to the skin preparation. A syringe with the drug dilution was attached to a 25 gauge needle, which was introduced through the skin at an angle of 10° with the bevel uppermost, until the lumen was covered. Sufficient solution was then injected to raise a 1–2 mm weal (0.01–0.02 ml). Normal saline was used as a control to exclude dermatographism, while 0.001% morphine sulphate in normal saline, which gives a weal and flare in all patients with normal cutaneous responsiveness, was used to assess whether a negative test was a result of impaired responsiveness. The intradermal test was recorded as positive when a weal of more than 0.8 cm arose within 10 min and persisted for 30 min or longer.

There was one departure from the intradermal testing protocol. This patient had an anaphylactic reaction to vecuronium with a positive skin test to vecuronium and a negative skin test to rocuronium. This patient had anaphylaxis to rocuronium at a subsequent anaesthetic and was tested a second time on the back rather than the forearm. A 1:1000 dilution of rocuronium 10 mg ml^{-1} in saline was used as the initial dilution. This patient has been described in detail previously.[13]

MCT assays were performed using commercially available kits (Pharmacia, Sydney, Australia). Each patient had blood taken by the referring anaesthetist and the serum was forwarded to our laboratory for testing. Because tryptase levels begin to rise within 30 min of an anaphylactic

Table 1 Drug dilutions used for intradermal testing

Drug	Standard dilution (1:1)	Dilution for testing
Rocuronium	10 mg ml^{-1}	1:1000
Pancuronium	2 mg ml^{-1}	1:1000
Vecuronium	4 mg ml^{-1}	1:1000
Atracurium	10 mg ml^{-1}	1:10 000
Cisatracurium	2 mg ml^{-1}	1:1000
Alcuronium	5 mg ml^{-1}	1:1000
Mivacurium	2 mg ml^{-1}	1:1000
Succinylcholine	50 mg ml^{-1}	1:1000
Alcuronium	5 mg ml^{-1}	1:1000
Gallamine	40 mg ml^{-1}	1:1000
Decamethonium	2 mg ml^{-1}	1:1000
Tubocurarine	10 mg ml^{-1}	1:10 000

Table 2 Diagnostic criteria and clinical features of 24 patients with anaphylaxis to rocuronium. CVS=cardiovascular system; Pos=positive; Neg=negative; ND=not done; Y=yes; N=no; U=unknown; M=male; F=female

Patient	Sex	Features						Past	Testing		
		CVS collapse	Pulmonary oedema	Bronchospasm	Angio-oedema	Rash	Flushing	exposure	Peak MCT	RIA	Intradermal
1	F	Y	N	N	N	N	Y	N	Pos	Pos	Pos
2	F	Y	N	Y	N	N	N	N	ND	Pos	Pos
3	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
4	F	Y	Y	Y	N	Y	N	U	Pos	Pos	ND
5	M	Y	N	N	N	N	Y	N	Pos	Pos	Pos
6	F	Y	N	N	N	Y	Y	N	Pos	Pos	Pos
7	F	N	N	Y	N	N	Y	N	Neg	Pos	Neg
8	M	Y	N	N	N	Y	N	U	Neg	Neg	Pos
9	F	Y	N	Y	N	N	Y	N	Pos	Pos	Pos
10	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
11	F	Y	N	Y	N	N	Y	N	ND	Pos	Pos
12	F	Y	N	N	N	N	N	Y	Neg	Neg	Pos
13	F	Y	N	N	N	N	N	N	Pos	Pos	Pos
14	M	Y	N	N	Y	Y	N	N	Pos	Pos	Pos
15	M	Y	N	N	N	N	N	N	Pos	Pos	Pos
16	F	Y	N	Y	N	N	Y	N	Pos	Pos	Pos
17	F	Y	N	N	Y	Y	N	N	Pos	Pos	Pos
18	F	Y	N	N	Y	N	Y	N	Pos	Pos	Pos
19	F	Y	N	Y	Y	Y	N	Y	Pos	Pos	Pos
20	F	Y	N	N	N	N	Y	N	Pos	Pos	Pos
21	F	Y	N	Y	N	N	N	N	Pos	Pos	Pos
22	M	N	N	Y	N	N	Y	N	ND	ND	Pos
23	F	Y	N	N	N	N	N	N	Pos	Pos	Pos
24	F	Y	Y	Y	N	N	Y	N	Pos	Pos	Pos

reaction and remain high for approximately 6 h, blood samples were taken between half an hour and 6 h after the reaction. In six patients with either a negative MCT or no MCT result, a convincing clinical picture of anaphylaxis together with a positive morphine RIA or intradermal test was considered sufficient to establish the diagnosis. It has been observed that tryptase assays can be elevated by causes other than anaphylaxis, such as vancomycin administration. In our study, however, all patients with a positive MCT also had corroborating clinical and laboratory evidence of anaphylaxis to rocuronium.

Morphine RIA testing was performed using morphine sulphate coupled to Sepharose to detect anti-quaternary ammonium IgE in serum. Morphine RIA is the most appropriate *in vitro* test for the detection of IgE antibodies that cross-react with substituted ammonium ions and hence for the *in vitro* diagnosis of NMBD-induced anaphylaxis.[8]

Results

In the period from 1997 to 1999 inclusive, we investigated 54 patients suspected to have had anaphylactic reactions to rocuronium and, of these, 24 fulfilled our criteria for anaphylaxis and admission to the database. Over many years, 386 other patients have been entered into the database after demonstrated anaphylaxis to other NMBDs, taking the total number of NMBD reactors to 410. The details of these 24 patients and the criteria for diagnosis are shown in Table 2. The clinical signs recorded resulted from detailed written descriptions of the suspected anaphylactic event by the anaesthetist attending the patient during the incident. Over the same period there were 10 other patients in New South Wales who fulfilled diagnostic criteria for anaphylaxis to rocuronium but were not admitted to the database as they were investigated by others. Only two of the 24 patients included were known to have received rocuronium previously.

Figure 1 shows the number of anaphylactic reactions attributed clinically and by testing to allergy to rocuronium by year from patients referred from within New South Wales. Anaphylaxis to rocuronium in New South Wales was first reported in 1997, the year after its release, and since then there has been an increase in the number of reports annually. This increase in reactions closely parallels the increase in usage. Equally, the observed reduction in the frequency of anaphylaxis caused by other NMBDs during this period is in keeping with the steady fall in market share of the other commonly used NMBDs.

Table 3 shows the incidence of skin test cross-reactivity to rocuronium in patients who reacted to other NMBDs. Figure 2 shows the relative propensity of each NMBD to cause positive intradermal tests in a population of known NMBD reactors. Table 4 gives the incidence of positive skin tests for other NMBDs in patients who reacted to rocuronium. Three patients showed cutaneous sensitivity to pancuronium, vecuronium and rocuronium but not to any other NMBD.

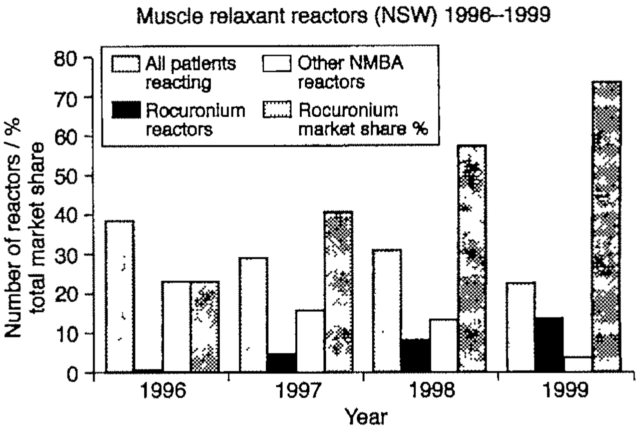

Fig 1 Anaphylaxis by year for rocuronium and other neuromuscular blocking drugs (as referred to senior author's clinic), and rocuronium market share in New South Wales, 1996–1999.

Table 3 Incidence of cross-reactivity of rocuronium with other NMBDs as determined by intradermal testing with rocuronium in patients allergic to another NMBD

Patients known to be allergic to	Number tested	Positive to rocuronium
Succinylcholine	44	10
Vecuronium	10	4
Atracurium/cisatracurium	13	0
Pancuronium	2	1
Alcuronium	1	1
Mivacurium	1	0

Discussion

As the incidence of anaphylactic reactions during anaesthesia is low, determining the risk of anaphylaxis to individual NMBDS would require a study of over 30 million patients.[2] Furthermore, for an individual drug, the estimated incidence of anaphylactic reactions will depend on the criteria for anaphylaxis used and the method and accuracy of determining drug usage and the number of reactions.

Fundamentally, the incidence of anaphylaxis to any particular NMBD will be determined by the market share (or number of uses) of the drug and the size of the population who are allergic, i.e. the number who have IgE antibodies to the drug.

The incidence of anaphylaxis to rocuronium closely follows the increase in usage of this NMBD (Fig. 1); the overall number of reactions and the number of reactions to other relaxants appears to be falling. This is reflected in data on patients seen at the Anaesthetic Allergy clinic between January and June 2000, among whom there were eight reactions to rocuronium and only three to all other NMBDs.

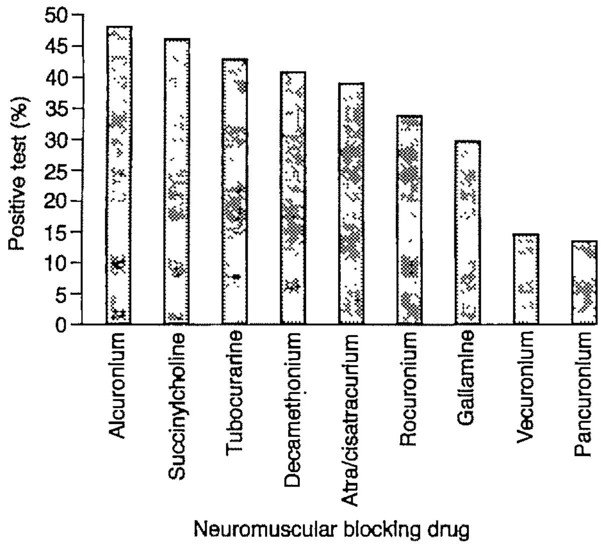

Fig 2 Incidence of positive intradermal tests to rocuronium and other neuromuscular blocking drugs in patients allergic to a neuromuscular blocker.

Table 4 Rocuronium reactors: positive skin tests to other NMBDs

NMBD	Tested	Positive	%
Succinylcholine	23	4	17.4
Vecuronium	23	4	17.4
Pancuronium	23	5	21.7
Atracurium/cisatracurium	23	11	47.8
Mivacurium	23	12	52.2

The reduction in reactions to other NMBDs is not a phenomenon reported or observed previously and is an important consideration in the relative safety of NMBDs. One would expect that if a drug of intermediate risk of producing anaphylaxis gained such a proportion of the market and displaced higher-risk drugs such as succinylcholine, the overall incidence of anaphylaxis should fall, and we suspect this is occurring with the increasing use of rocuronium in Australia.

There were 20 females and four males in our study, a female preponderance similar to that in patients allergic to other NMBDs in our database. This marked preponderance of females, usually of the order of 4:1, has been noted in other studies of anaphylaxis to NMBDs.[2 5 14 15]

RIA testing for morphine antibodies has now simplified RIA testing for NMBD allergy, as the single substituted ammonium group is common to the structures of both morphine and NMBDs. As a result, it is much more efficient to use the morphine RIA to test for IgE antibodies to NMBDs as a group than to use specific NMBD RIAs.[8]

A previous study[2] examined individual cutaneous relaxant sensitivity in a population of patients who reacted to NMBDs, and the results suggested that in Australia succinylcholine and alcuronium were high-risk drugs (over 40% of the NMBD-allergic population were sensitive) and vecuronium and pancuronium were low-risk drugs (fewer than 10% of NMBD-allergic patients were sensitive). These data appeared to reflect the described incidences of severe clinical reactions in the two large published series in Australia and France.[2 3]

Data from our analysis (Fig. 2) confirm these general trends. We have divided the NMBDs into high-, intermediate- and low-risk drugs in the population of relaxant-sensitive patients. These divisions, of course, are arbitrary and exact percentages of reaction depend very much on the sample size (number tested) for each drug. With the possible exception of decamethonium (only 10 tested, four positive) the numbers tested give a good indication of the relative risk of each agent. NMBDs with a high risk (>40%) of causing anaphylaxis in the relaxant-sensitive population were alcuronium, succinylcholine, *d*-tubocurarine and decamethonium. Intermediate-risk (20–40%) agents were atracurium/cisatracurium, rocuronium, mivacurium and gallamine. As expected, the two low-risk agents were vecuronium and pancuronium.

Allergy to NMBDs is due to the cross-linking of cell-bound IgE molecules by the substituted ammonium groups that provide the neuromuscular blocking effects of these drugs.[14] It is not, therefore, surprising that cross-sensitivity between NMBDs occurs. Indeed, it is more difficult to determine why patients allergic to one NMBD are not allergic to all NMBDs, yet of 410 patients allergic to NMBDs in the database only two had cutaneous sensitivity to all NMBDs tested.

The length of the carbon chain between active groups, the three-dimensional structure and the nature of binding of immunoglobulin may partially explain differences between individual agents. Differences in antigen–antibody binding strength may vary, but why this strength should be different when the antigen is so similar remains unclear. From previous data, cross-sensitivity between NMBDs has been estimated to occur in up to 60% of patients.[16 17]

We tested only a small number of reactors to other NMBDs with rocuronium to ascertain cross-sensitivity (Table 3). It is not possible to draw conclusions from these data, as the numbers tested were too small. It is interesting to observe, however, that the NMBDs with which there was some cross-reactivity included other members of the aminosteroid class of relaxants (such as vecuronium, pancuronium), to which rocuronium is most closely related structurally, and not the benzylisoquinolinium group, which includes atracurium, cisatracurium and mivacurium, which are structurally dissimilar to rocuronium.

When the known rocuronium reactors underwent skin tests to other NMBDs (Table 4), the results were not as expected. The incidence of cross-sensitivity to relaxants of the aminosteroid family was lower than that to the benzylisoquinolinium family. Structural similarity was expected to result in rocuronium reactors reacting most frequently with other relaxants of the aminosteroid family.

These results differ substantially from those of Laxenaire *et al.*,[5] which showed a very high incidence of cross-sensitivity using a 10^{-1} dilution of rocuronium (10 mg ml^{-1}) administered on the back. Levy *et al.*[18] studied weal and flare responses to cisatracurium and rocuronium on the forearm, and showed that concentrations such as those used by Laxenaire *et al.* produce a high incidence of false positives. It is generally believed that greater concentrations should be used on the back than on the forearm. However, in our experience there is minimal difference. Skin testing on the back using the same dilutions as those recommended for testing on the forearm is the standard method in New Zealand.

In conclusion, our experience suggests no cause for alarm about anaphylaxis to rocuronium. Our database shows that the rate of anaphylaxis is rising in proportion to usage of the drug, not out of proportion to it. Rocuronium is intermediate in reactivity in relaxant-sensitive patients.

The structure of rocuronium closely resembles that of the other aminosteroid NMBDs—vecuronium and pancuronium. Whilst rocuronium is not a high-risk agent in terms of anaphylaxis in the relaxant-sensitive population, it is significant that there is a distinct variation from its nearest relatives in its propensity to cause anaphylaxis in this population.

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References

1. Beard K, Jick H. Cardiac arrest and anaphylaxis with anesthetic agents [letter]. *J Am Med Assoc* 1985; **254**: 1742
2. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anaesthesia in Australia. *Ann Fr Anesth Reanim* 1993; **12**: 97–104
3. Laxenaire MC, Moneret-Vautrin DA, Widmer S, *et al.* Substances anesthesiques responsables de chocs anaphylactiques. Enquete multicentrique francaise. Anaesthetic drugs responsible for anaphylactic shock. French multi-center study. *Ann Fr Anesth Reanim* 1990; **9**: 501–6
4. Levy JH, Davis GK, Duggan J, *et al.* Determination of the hemodynamics and histamine release of rocuronium (ORG 9426) when administered in increased doses under N_2O/O_2-sufentanil anesthesia. *Anesth Analg* 1994; **78**: 318–21
5. Laxenaire MC, Gastin I, Moneret-Vautrin DA, Widmer S, Gueant JL. Cross reactivity of rocuronium with other neuromuscular blocking agents. *Eur J Anaesthesiol* 1995 (Suppl.); **11**: 55–64
6. Neal SM, Manthri PR, Gadiyar V, Wildsmith JA. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11
7. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; **14**: 17–21
8. Fisher MM, Baldo BA. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. *Anaesth Intensive Care* 2000; **28**: 167–170
9. Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991; **75**: 945–9
10. Fisher MM, Baldo BA. The diagnosis of fatal anaphylactic reactions during anaesthesia; employment of immunoassays for mast cell tryptase and drug-reactive IgE antibodies. *Anaesth Intens Care* 1993; **21**: 353–7
11. Fisher MM. Intradermal testing after anaphylactoid reaction to anaesthetic drugs; practical aspects of performance and interpretation. *Anaesth Intens Care* 1984; **12**: 115–20
12. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998: **80**: 26–9
13. Fisher MM, Merefield D, Baldo BA. Failure to prevent an anaphylactic reaction to a second anaesthetic drug during anaesthesia. *Br J Anaesth* 1999; **82**: 770–3
14. Laxenaire MC, Moneret-Vautrin DA, Guéant JL, *et al.* Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicentre epidemiological enquiry. *Ann Fr Anesth Reanim* 1993; **12**: 91–6
15. Youngman PR, Taylor KM, Wilson JD. Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; **2**: 597–9
16. Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; **306**: 262–6
17. Fisher M, Munro I. Life threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; **62**: 559–66
18. Levy J, Gottge M, Szlam F, Zaffer R, McCall C. Wheal and flare responses to rocuronium and atracurium in humans. *Br J Anaesth* 2000; **85**: 844–9

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BJA

LABORATORY INVESTIGATIONS

Effects of haemoglobin-based oxygen carrier Hemoglobin glutamer-200 (bovine) on intestinal perfusion and oxygenation in a canine hypovolaemia model

B. Driessen[1]*, J. S. Jahr[2], F. Lurie[2], S. M. Griffey[3] and R. A. Gunther[4]

[1]Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, New Bolton Center, Kennett Square, PA 19348, USA. [2]Department of Anaesthesiology and Pain Medicine, School of Medicine, University of California-Davis, Sacramento, CA 95817, USA. [3]Comparative Pathology Laboratory, Animal Resources Service, School of Veterinary Medicine, Davis, CA 95616, USA. [4]Department of Surgery, University of California-Davis Medical Center, Sacramento, CA 95817, USA

**Corresponding author: Department of Clinical Studies, New Bolton Center, School of Veterinary Medicine, University of Pennsylvania, 382 W. Street Rd, Kennett Square, PA 19348, USA*

The objective of this investigation was to study the effects of the first marketed haemoglobin-based oxygen carrier, Hemoglobin glutamer-200 (bovine) (Hb-200) (Oxyglobin®) on splanchnic perfusion and oxygenation in a canine model of acute hypovolaemia. Twelve anaesthetized dogs [mean weight 30.8 (S.D. 1.4) kg] were instrumented for recordings of heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output and cranial mesenteric arterial (CMA) and venous blood flows (CMV). Total and plasma haemoglobin (Hb), oxygen content and saturation, lactate concentration, pH and blood gases were analysed in arterial, mixed venous and mesenteric venous blood samples. Measurements were made before (baseline) and after 1 h of haemorrhage, after which animals were resuscitated with either shed blood (controls) or Hb-200 until HR, MAP and CVP returned to prehaemorrhage levels. Recordings were repeated immediately and 3 h after termination of fluid resuscitation, after which organ specimens were obtained for microscopic examination. Haemorrhage (average 32 ml kg^{-1}) reduced MAP to 50 mm Hg, increased HR and systemic vascular resistance (SVR), and was accompanied in both the systemic and the splanchnic circulation by significant decreases in blood flow, Hb content and oxygen delivery (DO_2), and lactic acidosis. In controls, all variables recovered to baseline after isovolaemic resuscitation with shed blood. In dogs resuscitated with a small volume of Hb-200 (10 ml kg^{-1}), HR, MAP, CVP and CMA and CMV blood flows returned to baseline. However, cardiac output, total Hb, oxygen content and systemic and mesenteric DO_2 remained depressed while SVR increased further. Mesenteric and systemic acid–base status recovered in both groups, and there was no difference in microscopic tissue damage between groups. Thus, Hb-200 reconstituted splanchnic perfusion and oxidative metabolism in spite of pronounced systemic vasoconstriction and insufficient restoration of CO and DO_2; it may improve diffusive oxygen transport in the microvasculature by virtue of haemodilution and its high efficiency in the uptake and release of oxygen.

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Severe haemorrhage is associated with redistribution of cardiac output, increasing oxygen delivery to some vital organs (brain, heart) but reduced delivery to others, such as the gut.[1 2] Mesenteric ischaemia is a major factor involved in impaired function of the intestinal mucosal barrier[3] and may contribute to the initiation of the septic inflammatory

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response syndrome.[4 5] Therefore, restoration of splanchnic perfusion in addition to the normalization of global perfusion is an important goal of resuscitation in hypovolaemia.[4]

Allogeneic and xenogeneic, stroma-free, ultrapurified haemoglobin solutions combine volume-expanding and oxygen-carrying capacities, making them potentially superior candidates for volume resuscitation in hypovolaemic patients.[6–9] However, most haemoglobin-based oxygen carriers (HBOCs) exert profound vasoconstrictive actions.[6–8] While a vasopressor effect may be advantageous for the body as a whole during hypovolaemic shock,[7] it might prolong the impairment of regional blood flow and oxygen delivery.[10–12] Animal studies are inconclusive, some providing evidence for improved gut perfusion[11 13–15] while others do not.[10–12]

Hemoglobin glutamer-200 (bovine) (Hb-200) (Oxyglobin®; Biopure, Cambridge, MA, USA) is an ultrapure solution of highly polymerized bovine haemoglobin.[6] It has been approved by the US Federal Drug Administration for the treatment of anaemia in dogs.[16] Hb-200 shares most of the properties of HBOC-201 (Hemopure®; Biopure),[6] the proposed human oxygen carrier currently under Phase III clinical investigation. In humans, both diaspirin-crosslinked human haemoglobin and polymerized bovine haemoglobin solutions have been associated with mild to moderate increases in plasma transaminases and pancreatic enzymes, and gastrointestinal symptoms.[7] Likewise, dogs may develop abdominal discomfort, peritoneal effusion and pancreatitis after infusion of Hb-200.[16] These signs may reflect impaired gut perfusion, considering the significant vasoconstrictive action of bovine haemoglobin solutions in both dogs and man.[17–19] We studied the effects of Hb-200 on mesenteric perfusion and oxygenation in a canine model of acute haemorrhage and compared the results with effects on the systemic circulation.

Methods

Twelve healthy, adult, mongrel dogs [mean weight 30.8 (SD 1.4) kg; seven female, five male) were studied after approval by the Campus Animal Care and Use Committee and in compliance with the Guide for the Care of Laboratory Animals (National Institutes of Health publication 86–23, revised 1985).

Animal preparation and instrumentation

Dogs were premedicated with oxymorphone 0.02 mg kg^{-1} i.m. and atropine 0.02 mg kg^{-1} i.m., and the cephalic vein was then catheterized percutaneously for continuous infusion of lactated Ringer's solution at the rate of 10 ml kg^{-1} h^{-1} throughout the preparation and instrumentation period and for administration of drugs. Anaesthesia was induced with propofol 2–4 mg kg^{-1} i.v. and diazepam 0.5 mg kg^{-1} i.v., and the animals were then intubated orotracheally and maintained with a balanced anaesthesia protocol, including isoflurane and fentanyl, to minimize potential confounding haemodynamic effects.[20] During animal preparation and instrumentation, isoflurane in oxygen was delivered at an end-tidal concentration of 0.8–1.2%, and fentanyl was infused at the rate of 0.7 μg kg^{-1} min^{-1} after an initial i.v. bolus of 10 μg kg^{-1}.[20] The lungs were ventilated mechanically with an anaesthesia ventilator (Model 2000; Hallowell EMC, Pietsfield, MA, USA), using tidal volumes (V_T) of 12–15 ml kg^{-1} and a respiratory rate of 9–11 breaths per minute to ensure an arterial partial pressure of carbon dioxide (Pa_{CO_2}) in the range of 35–45 torr (4.6–6.0 kPa). End-tidal partial pressure of carbon dioxide PE'_{CO_2}, end-tidal concentration of isoflurane (ISO$_{ET}$) and inspired oxygen concentration (FI_{O_2}) were monitored continuously using a Datex 254 airway gas monitor (Datex, Helsinki, Finland).

Further instrumentation included placement of catheters into the dogs' lateral saphenous vein and both femoral arteries for drug and fluid administration, blood withdrawal, and determination of systemic arterial pressures. An 8-Fr balloon-tipped, flow-directed thermodilution pulmonary arterial catheter (OptiQ; Abbott Laboratories, Chicago, IL, USA) was inserted via the jugular vein and floated into the pulmonary artery under direct monitoring of the pressure traces for measurements of central venous pressure (CVP), pulmonary artery occlusion pressure (POP), core body temperature and cardiac output. The pulmonary arterial catheter was connected to a cardiac output computer (Critical Care Systems QVUE, Oximetrix 3; Abbott Laboratories, Chicago, IL, USA) for continuous monitoring of cardiac output. Cardiac output was also assessed by thermodilution in triplicate using 10 ml of saline at room temperature. Body temperature was maintained between 38° and 39°C by means of a heating pad and circulating warm air blanket (Bair Hugger Model 505; Augustine Medical, Eden, MN, USA).

Dogs were splenectomized after a midline laparotomy to prevent release of sequestered red blood cells during sympathetic stimulation. Subsequently, the cranial mesenteric artery (CMA) was identified and exposed just distal to its origin at the abdominal aorta by bluntly dissecting through surrounding mesenteric and perivascular tissue. The CMA was encircled by a 4 mm Doppler transit-time flow probe (Transonics, Ithaca, NY, USA) approximately 1 cm distal to its origin. Using a similar technique, the triangle between portal and cranial mesenteric vein (CMV) was identified, and the CMV was encircled with a 6 mm Doppler transit-time flow probe (Transonics) 1–2 cm upstream to the CMV–portal junction. Flow probes were connected to a two-channel ultrasonic blood flow meter (T201; Transonics). Finally, a tributary of the CMV was cannulated with a 20 gauge catheter, which was then advanced into the CMV 4–5 cm upstream of the flow probe to allow mesenteric venous blood sampling.

Measured variables

Measured variables included heart rate (HR), mean arterial blood pressure (MAP), CVP, POP, cardiac output (as determined by thermodilution), and CMA and CMV blood flow. Arterial, mixed venous and mesenteric venous blood samples were collected intermittently from the femoral artery, right atrium and CMV respectively. Immediately after collection, blood samples were sealed and stored on ice. Subsequently, mixed venous (vHb_{total}) and mesenteric venous total haemoglobin ($mvHb_{total}$), and mixed venous plasma met-haemoglobin (Met-Hb) concentrations were measured in these samples using a Nova co-oximeter (Nova Biomedical, Waltham, MA, USA), and arterial, mixed venous and mesenteric venous oxygen contents (Ca_{O_2}, Cv_{O_2} and Cmv_{O_2} respectively) were measured directly in duplicate using an oxygen-specific electrode (LEXO$_2$CON-K; Hospex Fiberoptics, Chestnut Hill, MA, USA). Mixed venous and mesenteric venous lactate concentrations were determined in duplicate by means of a lactate analyser (Model 1500; YSI, Yellowsprings, OH, USA). Mixed venous and mesenteric venous pH (pH_v, pH_{mv}) and partial pressures of carbon dioxide (Pv_{CO_2} and Pmv_{CO_2} respectively) were analysed with a blood gas analyser (Model 170, Corning Medical, Medfield, MA). Blood gas values were corrected for the body temperature of the animals at the time of sampling. Mixed venous and mesenteric venous oxygen saturation (Sv_{O_2}, Smv_{O_2}) and standard base excesses (SBE_v, SBE_{mv}) were calculated by the blood gas analyser. All laboratory analysers used for determinations of oxygenation variables were validated for use with HBOCs.[21]

Body surface area (BSA, in square metres) was determined as (10.1 × [body weight in grams]$^{2/3}$)/10 000. Systemic vascular resistance (SVR) was calculated as ([MAP − CVP] × 79.9/(cardiac output/BSA); systemic oxygen delivery (sD_{O_2}) as Ca_{O_2} × cardiac output; mesenteric oxygen delivery (mD_{O_2}) as Ca_{O_2} × CMA blood flow; systemic oxygen consumption (sV_{O_2}) as ($Ca_{O_2} - Cv_{O_2}$) × cardiac output; mesenteric oxygen consumption (mV_{O_2}) as ($Ca_{O_2} - Cmv_{O_2}$) × CMA blood flow; systemic oxygen extraction ratio ($sExv_{O_2}$) as sV_{O_2}/sDv_{O_2}; and mesenteric oxygen extraction ratio ($mExv_{O_2}$) as mV_{O_2}/mD_{O_2}.

Experimental protocol

After completion of the surgical procedure, the infusion of lactated Ringer's solution was discontinued and the inspired gas switched from a source of 100% oxygen to medical air (FI_{O_2} 21–22%). For the remainder of the experiment, anaesthesia was maintained with end-tidal concentrations of isoflurane 0.7–0.8% [corresponding to 0.5–0.6 times the minimum alveolar concentration of isoflurane in dogs (~1.32 vol%)][22] and an infusion of fentanyl at a reduced rate of 0.4 μg kg^{-1} min^{-1} to take into account the lack of further surgical stimulation and to compensate for potential changes in fentanyl pharmacokinetics during hypovolaemia.[23] After these adjustments the dogs were allowed to stabilize for 45 min (equilibration period), and then all measurements (baseline) were taken. Subsequently, approximately 40% of the dogs' blood volume, which was estimated as 85 ml kg^{-1} body weight,[24] was withdrawn simultaneously from the lateral saphenous vein and femoral artery until an MAP of about 50 mm Hg was reached; shed blood was collected in citrate-containing bags and weighed. Additional small amounts of blood were removed to maintain the blood pressure at 50 mm Hg for 60 min. Cardiac output decreased by more than 50% from baseline during haemorrhage. At the end of the hypovolaemic period, all measurements were repeated (post-haemorrhage) and then dogs were allocated randomly to receive either shed blood at the rate of 30 ml kg^{-1} h^{-1} (control group) or Hb-200 (for details see Table 1) at the manufacturer's recommended infusion rate of 10 ml kg^{-1} h^{-1} (corresponding to 1.3 g kg^{-1} h^{-1} of bovine haemoglobin). Transfusion of shed blood or Hb-200 was discontinued once HR, MAP and CVP had returned to baseline and stabilized. All measurements were repeated immediately and 3 h after fluid resuscitation had been terminated. Animals were euthanized without regaining consciousness after the last measurements by means of an overdose of potassium chloride, and underwent post-mortem necropsy.

Histopathology

Immediately after death, specimens from the lung, kidney, liver, pancreas, mesenteric lymph nodes, duodenum, jejunum, ileum, colon and caecum were taken for microscopic examination, and transferred to 10% neutral buffered formalin solution. Tissues were then processed routinely to paraffin blocks and 5 μm sections were stained with haematoxylin and eosin. Interpretation was performed by a pathologist (SMG), who was blinded to the study groups.

Table 1 Specifications of Hemoglobin glutamer-200 (bovine) (Hb-200). All data except colloid oncotic pressure and P_{50} provided by manufacturer. [a]Measured with Colloid Oncometer 4420 (Wescor, Logan, UT, USA). P_{50} is the oxygen tension at which the polymerized bovine haemoglobin molecule is half saturated with oxygen.

Polymerized bovine haemoglobin	13 g dl^{-1}
NaCl	113 mmol litre^{-1}
KCl[1]	4 mmol litre^{-1}
CaCl-2H$_2$O	1.4 mmol litre^{-1}
NaOH	10 mmol litre^{-1}
Na-lactate	27 mmol litre^{-1}
N-acetyl-L-cysteine	200 mg dl^{-1}
Osmolality	300 mosm kg^{-1}
pH	7.8
Colloid oncotic pressure[a]	42 torr (5.6 kPa)
P_{50}[39]	34 torr (4.5 kPa)
Unpolymerized haemoglobin	< 5%
Molecular weight of ~50% of haemoglobin polymers	65–130 kDa
Molecular weight of ≤10% of haemoglobin polymers	>500 kDa
Free glutaraldehyde	<3.5 μg ml^{-1}
Endotoxin	<0.05 EU ml^{-1}

Table 2 Effects of haemorrhage and subsequent resuscitation with autologous blood (control) or Hemoglobin glutamer-200 (bovine) (Hb-200) on systemic haemodynamic variables. Variables determined were heart rate (HR), cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary arterial occlusion pressure (POP) and systemic vascular resistance (SVR). Values are mean (SEM) for six dogs in each group. Resuscitation I=immediately after transfusion of autologous blood; Resuscitation II=3 h after transfusion of autologous blood. Significant differences from baseline values: *$P<0.05$; **$P<0.01$. Significant differences between control and Hb-200 group: $^{\dagger}P<0.05$; $^{\dagger\dagger}P<0.01$

Variable	Resuscitation group	Baseline	After haemorrhage	Resuscitation	
				I	II
HR (min^{-1})	Control	113 (6)	211 (8)**	122 (14)	96 (5)
	Hb-200	104 (7)	195 (9)**	127 (13)	139 (28)†
CO (litre min^{-1})	Control	3.4 (0.3)	1.5 (0.3)**	3.8 (0.3)	3.8 (0.2)
	Hb-200	3.0 (0.2)	1.3 (0.2)**	2.3 (0.2)*††	1.8 (0.2)**††
MAP (mm Hg)	Control	95 (4)	54 (1)**	83 (8)	99 (4)
	Hb-200	87 (6)	48 (3)**	92 (3)††	80 (13)
CVP (mm Hg)	Control	4 (1)	3 (2)	6 (2)	6 (1)
	Hb-200	3 (1)	0 (1)	4 (2)	3 (1
POP (mm Hg)	Control	5 (1)	4 (1)	6 (1)	7 (1)
	Hb-200	3 (1)	2 (1)	3 (1)	3 (2)
SVR	Control	2303 (362)	3239 (631)**	1611 (128)*	1998 (177)
(dynes s^{-1} cm^{-5})	Hb-200	2307 (144)	3100 (281)**	3169 (207)*††	3549 (286)*††

Statistical analysis

Results are given as arithmetic mean (SEM). Statistical evaluation of data within each group (i.e. testing for differences between time points) included analysis of variance (ANOVA) for repeated measures. When ANOVA indicated significant differences, statistical testing was followed by comparisons between baseline and time points using a Student's *t*-test for independent samples and *post hoc* Bonferroni correction. Statistical evaluation of data between both groups was performed using an ANOVA for repeated measures followed by the *t*-test. $P<0.05$ was taken to be statistically significant.

Results

Haemodynamic, oxygenation and acid–base variables

No statistically significant differences in systemic and mesenteric haemodynamic, oxygenation and acid–base variables measured before haemorrhage (baseline) were observed between groups (Tables 2–4; Figs 1–3). The depth of anaesthesia (as judged by jaw tone, palpebral reflex and lack of motor response to intermittent toe pinch stimulation), ventilation and arterial oxygen saturation remained unchanged throughout the experiment.

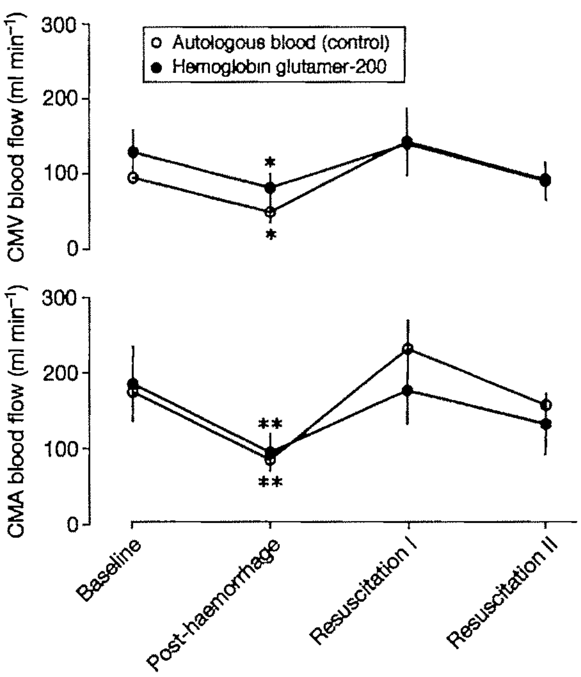

Fig 1 Cranial mesenteric arterial (CMA) and venous (CMV) blood flow in anaesthetized dogs at baseline (end of equilibration), 60 min after haemorrhage (end of hypovolaemia) and immediately (Resuscitation I) and 3 h (Resuscitation II) after transfusion of autologous blood (control) and Hemoglobin glutamer-200 (bovine). Values are mean (SEM) for six dogs in each group. Significant differences from baseline values: *$P<0.05$; **$P<0.01$.

Approximately 40% of the estimated blood volume[24] was withdrawn in the control and Hb-200 groups [31.6 (4.1) and 31.5 (4.1) ml kg^{-1} respectively] to reduce MAP to the set point of approximately 50 mm Hg. Haemorrhage resulted in a decline in vHb_{total} and Ca_{O_2} of approximately 20 and 18% respectively (Table 3). Dogs in both groups responded to the acute blood loss as expected and to the same extent (Tables 2–4; Figs 1–3). Cardiac output (Table 2), CMA blood flow, CMV blood flow (Fig. 1), systemic oxygen delivery (sD_{O_2}) and mesenteric oxygen delivery (mD_{O_2}) (Fig. 2) decreased on average by 56, 50, 43, 65 and 58% respectively. HR and SVR increased by an average of 87 and 38% respectively (Table 2). Central venous pressure and POP decreased immediately after haemorrhage, but at the end of the hypovolaemic period, when post-haemorrhage values were recorded, this effect was not statistically significant (Table 2). sDv_{O_2} and mDv_{O_2} were equally diminished after haemorrhage (Fig. 2), and mixed venous and mesenteric blood oxygenation variables were signifi-

Table 3 Effects of haemorrhage and subsequent resuscitation with autologous blood (control) or Hemoglobin glutamer-200 (bovine) (Hb-200) on systemic and mesenteric oxygenation variables and total haemoglobin. Variables measured were arterial blood oxygen content (Ca_{O_2}), arterial oxygen saturation (Sa_{O_2}), mixed venous blood total haemoglobin content (vHb_{total}) and oxygen content (Cv_{O_2}), oxygen saturation (Sv_{O_2}), mesenteric venous blood total haemoglobin content ($mvHb_{total}$) and oxygen content (Cmv_{O_2}), and oxygen saturation (Sv_{O_2}, Smv_{O_2}). Systemic and mesenteric oxygen consumption (sV_{O_2}, mV_{O_2}) were calculated. Values are mean (SEM) for six dogs in each group. Resuscitation I=immediately after transfusion of autologous blood; Resuscitation II=3 h after transfusion of autologous blood. Significant differences from baseline values: *$P<0.05$; **$P<0.01$. Significant differences between control and Hb-200 group: †$P<0.05$; ††$P<0.01$. Significant differences between mixed venous and mesenteric venous blood: ‡$P<0.05$; ‡‡$P<0.01$.

Variable	Resuscitation group	Baseline	After haemorrhage	Resuscitation	
				I	II
Ca_{O_2} (ml dl^{-1})	Control	19.2 (0.6)	16.5 (1.2)*	18.7 (0.8)	19.0 (0.6)
	Hb-200	20.3 (0.5)	16.1 (0.8)**	16.8 (0.6)*†	16.9 (0.8)*†
Sa_{O_2} (%)	Control	97.9 (0.6)	96.5 (1.1)	97.7 (0.5)	97.5 (0.6)
	Hb-200	95.9 (0.5)	95.2 (0.5)	96.5 (0.5)	96.7 (0.5)
vHb_{total} (g dl^{-1})	Control	14.5 (1.8)	11.8 (1.9)**	13.8 (1.5)	14.5 (1.6)
	Hb-200	15.2 (1.3)	11.8 (1.3)**	11.5 (0.9)**†	12.3 (2.0)*†
Cv_{O_2}(ml dl^{-1})	Control	16.0 (0.7)	7.4 (2.1)**‡	15.2 (0.9)	16.4 (0.9)
	Hb-200	15.6 (0.7)	6.6 (1.0)**‡	9.4 (0.6)**††‡	9.6 (1.4)**††
Sv_{O_2} (%)	Control	81.7 (0.6)	37.9 (2.4)**‡‡	82.2 (1.2)	78.6 (1.5)
	Hb-200	74.1 (3.1)	38.8 (5.1)**‡‡	59.5 (1.6)*††‡‡	46.6 (7.8)*††‡
sV_{O_2} (ml min^{-1})	Control	108 (44)	134 (29)	131 (21)	96 (24)
	Hb-200	137 (12)	122 (16)	168 (16)	135 (28)
$mvHb_{total}$ (g dl^{-1})	Control	14.7 (1.6)	11.8 (1.3)**	13.6 (1.6)*	14.7 (1.8)
	Hb-200	15.4 (1.8)	12.0 (1.3)**	11.8 (0.6)**†	12.1 (1.6)**†
Cmv_{O_2} (ml dl^{-1})	Control	16.4 (0.7)	9.3 (1.6)**	15.8 (1.0)	16.4 (0.9)
	Hb-200	15.6 (0.7)	8.6 (0.5)**	10.9 (0.6)**††	10.8 (1.4)**††
Smv_{O_2} (%)	Control	87.3 (2.9)	55.8 (9.7)**	85.9 (1.2)	80.3 (3.6)
	Hb-200	79.4 (4.2)	49.4 (3.1)**	70.0 (2.8)*†	60.0 (10.4)*†
mV_{O_2} (ml min^{-1})	Control	5.0 (1.2)	5.6 (1.1)	6.4 (1.5)	3.8 (0.7)
	Hb-200	5.9 (1.2)	7.5 (2.2)	12.0 (3.6)	7.4 (2.2)

cantly reduced (Table 3). The mixed venous oxygen content (Cv_{O_2}) and saturation (Sv_{O_2}) decreased rapidly by an average of 56 and 51% respectively, and in parallel but to a lesser degree, mesenteric venous oxygen content (Cmv_{O_2}) and saturation (Smv_{O_2}) declined by 50 and 37% respectively (Table 3). Systemic (sV_{O_2}) and mesenteric (mV_{O_2}) oxygen consumption did not change in either group during hypovolaemia; however, oxygen extraction in the systemic and mesenteric vascular bed increased to 2.9 and 2.6 times the baseline value respectively (Table 3; Fig. 3). Oxygen extraction was significantly greater in the systemic than mesenteric circulation (Fig. 3). There was no difference between groups in this increase in oxygen extraction ratios, and there was also no difference between groups in the degree of ischaemia-induced lactate acidosis that developed during the post-haemorrhage phase (Table 4).

Whereas the infusion of 10 ml kg^{-1} Hb-200 was as effective as a three times larger volume of autologous blood (average 32 ml kg^{-1}) in returning HR, MAP and CVP to prehaemorrhage levels (Table 1), this treatment, in contrast to shed blood transfusion, failed to restore other systemic haemodynamic, blood and oxygen variables (Figs 1–3; Tables 2 and 3). In the Hb-200 group, cardiac output, vHb_{total}, Ca_{O_2}, Cv_{O_2}, Sv_{O_2} and sD_{O_2} all remained significantly below and SVR and systemic oxygen extraction remained significantly above baseline values throughout the entire post-resuscitation period (Figs 1–3; Tables 2 and 3). Systemic oxygen consumption (sV_{O_2}) was not significantly affected, though a trend for an increase was recognized in

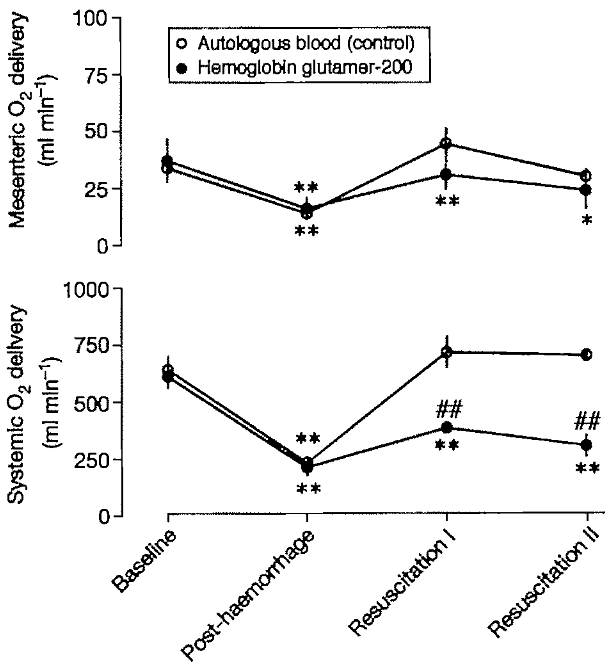

Fig 2 Systemic and mesenteric oxygen delivery in anaesthetized dogs at baseline (end of equilibration), 60 min after haemorrhage (end of hypovolaemia), and immediately (Resuscitation I) and 3 h (Resuscitation II) after transfusion of autologous blood (control) or Hemoglobin glutamer-200 (bovine). Values are mean (SEM) for six dogs in each group. Significant differences from baseline values: *$P<0.05$; **$P<0.01$. Significant differences between control and Hb-200 groups: ##$P<0.01$.

Table 4 Effects of haemorrhage and subsequent resuscitation with autologous blood (control) or Hemoglobin glutamer-200 bovine (Hb-200) on blood acid–base variables. Variables determined were mixed venous pH (pH_v), partial pressure of carbon dioxide (Pv_{CO_2}), standard base excess (SBE_v) and lactate ($Lactate_v$), and mesenteric venous pH (pH_{mv}), partial pressure of carbon dioxide (Pmv_{CO_2}), standard base excess (SBE_{mv}) and lactate concentration ($Lactate_{mv}$). Partial pressures of carbon dioxide are also given in SI units (kPa, square brackets). Values are mean (SEM) for six dogs in each group. Resuscitation I=immediately after transfusion of autologous blood; Resuscitation II=3 h after transfusion of autologous blood. Significant differences from baseline values: *$P<0.05$; **$P<0.01$

Variable	Resuscitation group	Baseline	After haemorrhage	Resuscitation	
				I	II
pH_v	Control	7.35 (0.01)	7.16 (0.02)**	7.24 (0.02)**	7.36 (0.03)
	Hb-200	7.36 (0.01)	7.22 (0.02)**	7.28 (0.01)**	7.29 (0.06)
Pv_{CO_2}(torr)	Control	43.0 (1.7)	61.1 (2.2)**	50.7 (2.1)**	41.7 (2.3)
(kPa)		5.7 (0.2)	8.1 (0.3)	6.8 (0.3)	5.6 (3.1)
	Hb-200	40.4 (1.2)	56.4 (2.4)**	48.3 (1.2)**	47.2 (4.2
		5.4 (0.2)	7.5 (0.3)	6.4 (0.2)	6.3 (0.6)
SBE_v (mmol litre^{-1})	Control	–1.7 (0.4)	–8.3 (0.9)**	–6.6 (1.4)*	–1.2 (1.5)
	Hb-200	–2.2 (0.6)	–6.0 (0.6)**	–4.0 (0.5)*	–4.2 (2.6)
$Lactate_v$ (mmol litre^{-1})	Control	1.41 (0.17)	3.61 (0.38)**	2.19 (0.10)**	1.53 (0.24)
	Hb-200	1.18 (0.23)	2.87 (0.50)**	2.09 (0.18)**	2.57 (1.45)
pH_{mv}	Control	7.37 (0.02)	7.19 (0.02)**	7.26 (0.02)**	7.37 (0.03)
	Hb-200	7.35 (0.01)	7.22 (0.01)**	7.29 (0.01)**	7.30 (0.07)
Pmv_{CO_2}(torr)	Control	41.8 (1.8)	55.4 (3.8)**	47.0 (1.3)**	41.5 (1.5)
(kPa)		5.6 (0.2)	7.4 (0.5)	6.3 (0.2)	5.5 (0.2)
	Hb-200	41.0 (1.9)	55.0 (1.4)**	48.4 (1.2)**	46.4 (4.7
		5.5 (0.3)	7.3 (0.2)	6.5 (0.2)	6.2 (0.6)
SBE_{mv} (mmol litre^{-1})	Control	–0.9 (0.4)	–7.9 (0.7)**	–6.2 (1.0)*	–1.0 (1.3)
	Hb-200	–2.3 (1.0)	–5.9 (0.7)*	–3.9 (0.4)*	–4.3 (2.9)
$Lactate_{mv}$ (mmol litre^{-1})	Control	1.29 (0.24)	3.34 (0.47)**	2.01 (0.12)*	1.62 (0.27)*
	Hb-200	1.34 (0.27)	2.77 (0.56)**	2.14 (0.08)*	3.33 (1.42)**

the Hb-200 group immediately after resuscitation. Unlike in the systemic circulation, blood flow in the CMA and CMV returned to baseline after Hb-200 infusion (Fig. 1). However, oxygen delivery did not recover completely in this vascular bed (maximum 82% of baseline) (Fig. 2) after Hb-200 infusion, and Cmv_{O_2} and Smv_{O_2} values remained significantly below baseline recordings and measurements in control dogs (Table 3). When compared with prehaemorrhage values and controls, mesenteric oxygen extraction (35–37%) remained markedly elevated in Hb-200-treated dogs, though less so than systemic oxygen extraction (43–44%; Fig. 3). Within each group, mixed venous (vHb_{total}) and mesenteric venous ($mvHb_{total}$) total haemoglobin concentrations did not differ from each other after resuscitation, but the Hb-200 group values were significantly lower than in controls (Table 3) despite an increase in the plasma concentration of haemoglobin in this group from zero to 2.9 (0.1) g dl^{-1} immediately after resuscitation and 2.5 (0.1) g dl^{-1} 3 h after resuscitation. There was no difference in the Met-Hb fraction between the control and Hb-200 groups at any time throughout the experiment; immediately and 3 h after resuscitation, the Met-Hb fraction was 0.2 (0.0) and 0.3 (0.0)% respectively in controls and 0.3 (0.1) and 0.4 (0.1)% in Hb-200-treated dogs.

After resuscitation, the control and Hb-200-treated animals did not differ in their mesenteric or systemic acid–base status (Table 4). At the end of the observation period, all acid–base variables listed in Table 4 had returned to prehaemorrhage levels, except the lactate concentration in mesenteric venous blood of both groups.

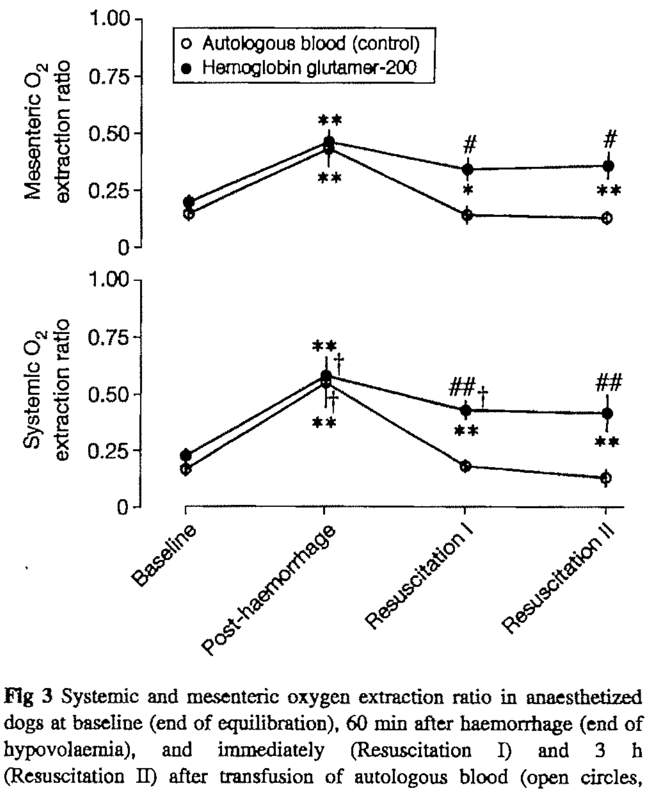

Fig 3 Systemic and mesenteric oxygen extraction ratio in anaesthetized dogs at baseline (end of equilibration), 60 min after haemorrhage (end of hypovolaemia), and immediately (Resuscitation I) and 3 h (Resuscitation II) after transfusion of autologous blood (open circles, control) or Hemoglobin glutamer-200 (bovine) (closed circles). Values are mean (SEM) for six dogs in each group. Significant differences from baseline values: *$P<0.05$; **$P<0.01$. Significant differences between control and Hb-200 groups: #$P<0.05$; $P<0.01$. Significant differences between systemic and mesenteric oxygen extraction: †$P<0.05$.

Table 5 Histomorphological changes after haemorrhage and subsequent resuscitation with autologous blood (control) or Hemoglobin glutamer-200 bovine (Hb-200). Immediately after the experiment, necropsy specimens were taken for microscopic examination from the intestine, including duodenum, jejunum, ileum, colon and caecum, mesenteric lymph nodes, pancreas, liver, kidneys and lungs. A blinded examiner then evaluated the tissues. Values given are the number of dogs in the control group (resuscitation with autologous blood) and Hb-200 group (resuscitation with Hemoglobin glutamer-200 bovine]) in which the microscopic changes recorded were found

Tissue	Morphological changes	No. of dogs per group	
		Control	Hb-200
Intestines	Acute epithelial necrosis/sloughing	6	5
	Congestion of lamina propria	0	1
	Submucosal haemorrhage and/or congestion	1	1
Mesenteric lymph node	Scattered medullary erythrophagocytosis	2	5
Pancreas	Focal areas of acute necrosis	0	1
Liver	Mild periportal neutrophilic infiltration	0	2
	Sinusoidal congestion with neutrophilic infiltrates	1	1
	Portal bile duct stasis	0	1
	Multifocal subcapsular necrosis with haemorrhage and neutrophilic infiltrates	1	0
Kidney	Mild chronic interstitial nephritis	0	1
	Congested glomeruli	0	1
Lung	Interstitial congestion	2	2

Histopathological findings

On necropsy, no macroscopically abnormal findings were recorded in any of the visceral organs examined except hyperaemia of intestinal organs and congestion of mesenteric blood vessels in both groups. Histological changes were observed in necropsy specimens from all dogs and are listed in Table 5. However, the only tissues that consistently showed changes were from the gastrointestinal tract. In both groups, the gastrointestinal tract had acute mucosal damage in all or parts of the duodenum, jejunum, ileum, colon and caecum, consisting of epithelial cell necrosis and sloughing. The occurrence of red blood cells in the cytoplasm of phagocytes residing in the mesenteric lymph nodes was the only morphological lesion with a markedly higher incidence in Hb-200-treated dogs.

Discussion

In a canine model of acute haemorrhage, we studied the restoration of systemic and gut perfusion and oxygenation, as well as morphological changes in the visceral organs after resuscitation with either autologous blood or an HBOC. Our data indicate that hypovolaemic resuscitation with Hb-200 reconstitutes mesenteric perfusion and oxidative metabolism in the early post-resuscitation period (Fig. 1; Tables 3 and 4) despite pronounced vasoconstriction in the systemic vasculature accompanied by low cardiac output and persistence of lower than normal systemic and mesenteric oxygen delivery (Table 2; Fig. 2).

The canine model of acute hypovolaemia used in this study is well characterized.[25–26] We decided to use a haemorrhage that decreased mean arterial pressure to 50 mm Hg, which was achieved with moderate blood loss (about 40% of circulating blood volume) in the control and study groups.[24] This method ensures a severe but not necessarily lethal insult that was similar to many clinical situations of acute blood loss. Under most clinical circumstances, fluid resuscitation is guided by measurements of HR, MAP and CVP.[27] We therefore used the return of these clinically most commonly measured variables to baseline as the endpoint for volume resuscitation, followed by a 3 h period for continued monitoring of the dogs.

In both groups of animals, all systemic haemodynamic, oxygenation and acid–base variables measured before haemorrhage were well within the normal range reported for dogs (Tables 2–4).[2 25 26] Likewise, mesenteric blood flow and oxygenation data at baseline were in accordance with those reported in dogs not undergoing laparotomy (Fig. 1; Table 3),[28 29] indicating an intact splanchnic circulation before haemorrhage. In the dog, progressive haemorrhage induces strong activation of the sympathetic nervous system and the subsequent redistribution of blood flow causes hypoperfusion in many organs, including the pancreas.[2 3 30] Also, gastrointestinal perfusion diminishes with haemorrhage, initially in proportion to the reduction in cardiac output,[2 30] but later out of proportion to the decrease in cardiac output as blood loss becomes more severe.[3] However, this decrease is primarily mediated by the activation of local renin–angiotensin mechanisms.[3] We observed similar haemodynamic responses to haemorrhage in the present experiment. MAP and cardiac output decreased substantially, and HR and SVR increased significantly (Table 2). Mesenteric arterial blood flow and oxygen delivery decreased in both groups to about the same extent as cardiac output (Figs 1 and 2; Tables 2 and 3), which is consistent with findings in pigs with similar haemorrhages.[11 15] Gut oxygen consumption was maintained because of a marked increase in oxygen extraction (Table 3; Fig. 3). The corresponding decrease in mesenteric venous oxygen saturation ($S\text{mv}_{O_2}$) was similar to that measured non-invasively in dogs after haemorrhage,[29] thus excluding a major effect of the preceding surgical procedure on gut blood flow and oxygenation. In both the systemic and splanchnic circulation, increased oxygen extraction failed to compensate entirely for insufficient oxygen delivery, and anaerobic metabolism therefore occurred. However, the resulting metabolic acidosis (Table 4) was mild enough that a possible further impairment of mesenteric blood flow due to any vasoconstrictive action of Hb-200 in the splanchnic system was likely to be recognized as a further deterioration in the acid–base variables.

Stroma-free haemoglobin solutions appear to be superior resuscitation fluids because they carry, deliver and release oxygen in a cooperative manner, and are highly oxygen-saturated at ambient oxygen pressures.[7 9] This applies particularly to bovine haemoglobin solutions (Hb-200, HBOC-201), which have a relatively high haemoglobin content (13 g dl^{-1}), low oxygen affinity and hence high oxygen off-loading capacity [P_{50} 34 torr (4.5 kPa)], and a relatively long plasma half-life (>20 h).[6 7 18] Furthermore, exercise physiology studies have suggested that these solutions have an efficacy ratio three times greater than erythrocyte-borne haemoglobin, on the basis of increments and decrements in oxygen diffusion capacity.[6] However, our data challenge this view. In contrast to isovolaemic resuscitation with autologous blood (controls), we did not find restoration of global oxygen delivery to prehaemorrhage levels by Hb-200, but instead significant systemic vasoconstriction and a lower cardiac output after administration of a volume one-third of that of blood loss (Table 2). Furthermore, total haemoglobin and arterial oxygen contents remained at the low post-haemorrhage level (Table 3). Thus, animals in the study group were systemically under-resuscitated despite HR, MAP and CVP returning to baseline. Cardiac output probably remained lower because of the increase in total peripheral vascular resistance caused by Hb-200 rather than because of volume underloading, because indicators of right (CVP) and left (POP) ventricular preload returned to baseline in this group also (Table 2). Significant decreases in cardiac output resulting from pronounced vasoconstriction have also been reported in dogs[19] and humans[18 31] undergoing isovolaemic haemodilution with polymerized bovine haemoglobin solutions. It is thought that scavenging of the endothelium-derived relaxing factor, nitric oxide, is the chief mechanism by which stroma-free haemoglobin elicits vasoconstriction, but the release of endothelin-1 and interaction with adrenoceptors and inositol triphosphate pathways may also be involved in this effect.[8] Unexpectedly, global tissue hypoxia resolved after low-volume resuscitation with Hb-200, as indicated by evaluation of mixed venous acid–base status (pH, SBE, lactate concentration).

Our data provide no evidence that Hb-200 compromised gastrointestinal perfusion and oxygenation significantly. CMA and CMV perfusion, unlike cardiac output, returned to the prehaemorrhage level after low-volume resuscitation with Hb-200 (Fig. 1). Blood flow in the CMA and CMV increased immediately after resuscitation by an average of 90 and 78% respectively from post-haemorrhage levels. Cardiac output increased to nearly the same extent (average 88%) (Table 2), suggesting that now the stroke volume was distributed in favour of the splanchnic system, which was probably the result of a lack of vasoconstrictive action by Hb-200 in this vascular bed. Total haemoglobin concentrations were similar in mesenteric and mixed venous blood (Table 3), which argues against a greater haemodilutional effect in the mesenteric vasculature and against increased flow through larger numbers of capillaries carrying just plasma. Hemoglobin glutamer-200 seems to behave similarly to diaspirin-crosslinked haemoglobin (DCLHb), pyridoxalated haemoglobin polyoxyethylene conjugate and stroma-free human haemoglobin solution, all of which improve intestinal blood flow after acute haemorrhage.[11 13–15] The systemic and regional haemodynamic effects of Hb-200 resemble particularly those of DCLHb, which increases vascular resistance in skeletal muscle but not in the gastrointestinal system, liver, kidney brain, heart or skin.[32] In contrast, recombinant human haemoglobin (rHb1.1), bovine fumaryl-crosslinked haemoglobin (ββHb) and αα-crosslinked haemoglobin (ααHb) reduce intestinal perfusion as much as perfusion of other organs.[10–12] Therefore, the effects of HBOCs on the splanchnic circulation may depend on the chemical modification technique used for tetramerization.

While splanchnic blood flow returned to the prehaemorrhage level in Hb-200-treated animals, oxygen delivery to the gut did not, because of a lack of increase in total blood haemoglobin and, hence, arterial oxygen content (Fig. 2; Table 3). As a result, mesenteric oxygen extraction remained significantly elevated and mesenteric venous oxygen saturation decreased significantly after resuscitation (Fig. 3; Table 3). This effect was significantly less pronounced in the intestinal than in the systemic circulation, reflecting the better correction of mesenteric arterial than systemic blood flow and oxygenation. This finding coincides with the improvement by DCLHb of gut microcirculation and mucosal oxygen tension after haemorrhagic shock.[13 15] Increased oxygen extraction in both small bowel and peripheral tissues sufficed to resolve the anaerobic metabolism that had occurred during hypovolaemia and to return the acid–base status to baseline (Table 4). Only lactate values remained slightly elevated, but they were similar to those of the control group (Table 4).

Although blood flow in the intestinal mucosa was not measured directly, microscopic examination of intestinal tissues did not reveal evidence of greater ischaemic damage in Hb-200-treated dogs than in animals transfused with whole blood. The lesions observed were similar in frequency and severity in the two groups and compatible with hypoxic injury caused by haemorrhagic shock (Table 5).[33] Hence, the clinically observed signs of abdominal discomfort, elevated plasma transaminases and pancreatitis after administration of HBOCs[7 16] may not be associated with any further ischaemic/hypoxic insult caused by these solutions. However, because animals did not recover from anaesthesia, survived only 3 h after resuscitation and were incompletely volume-resuscitated in the Hb-200 group, it remains speculative as to whether the microscopic changes seen in the gut and other visceral organs might have progressed with time, considering the long plasma half-life of bovine HBOCs (e.g. the $t_{1/2}$ of Hb-200 is 18–43 h).[6 16] Nonetheless, our results agree with previous studies in dogs, in which there were either no or only minor morphological changes in liver, kidney and lung biopsy specimens obtained 7 days[34] or 2 h[35] after HBOC infusion. The variable erythrophagocytosis within the mesenteric lymph nodes of both groups was probably related to manipulation during the experiments and, in the case of Hb-200, to uptake of the HBOC by the reticuloendothelial system.[6]

A surprising yet important finding of the present study was that systemic and regional tissue oxidative metabolism seemed to be reinstituted after low-volume resuscitation with Hb-200 despite sustained depression of cardiac output and low arterial oxygen delivery in both the systemic and the mesenteric circulation. Factors that may have contributed to this positive effect include better blood flow characteristics as a result of decreased blood viscosity, an increase in plasma oxygen transport capacity and improved oxygen diffusion from the blood into the tissues. Hemoglobin glutamer-200 has a viscosity three times lower that of than whole blood.[18] In addition, it has high colloid oncotic pressure (42 torr), which promotes haemodilution by intravascular fluid shifts. This was evident from a lack of increase in total haemoglobin after resuscitation despite an average increase of 2.9 g dl^{-1} in plasma haemoglobin concentration. Lower blood viscosity, and hence more homogeneous distribution of capillary flow, might have preferentially affected the perfusion of tissues in which vasoconstriction prevailed. In the intestinal mucosa, nutrient arterioles branch from their parent vessel at a right-angle. This microvascular pattern facilitates 'plasma skimming', a phenomenon characterized by a decrease in the effective haematocrit of blood as it passes through villous capillaries relative to the haematocrit measured in the systemic circulation.[3] As a result, the oxygen-carrying capacity of the blood may decrease selectively in the splanchnic microcirculation. The presence of an HBOC-like Hb-200 in blood plasma, however, will help minimize the impact of this effect on tissue oxygenation by virtue of its oxygen-carrying capacity. Theoretical analysis of oxygen release in the microcirculation,[36] as well as *in vitro*[37] and *in vivo* data,[17 18] suggest that the presence of free haemoglobin in plasma markedly increases the diffusion of oxygen from the blood into tissues. This appears to be even more important at a low haematocrit, when the spatial distance between erythrocytes increases and extracellular haemoglobin functions as a bridge for oxygen transfer from red blood cells to the endothelial membrane. The increased oxygen diffusion capacity of blood containing acellular bovine haemoglobin may be due to the low oxygen-binding affinity of bovine HBOCs (P_{50} 34 torr versus 28 for canine haemoglobin),[21] favouring oxygen release but not markedly affecting oxygen uptake[38], and their pronounced Haldane (carbon dioxide) and Bohr (pH) effects,[18] which augment oxygen off-loading, particularly in hypoxic tissues. Thus, it is likely that in Hb-200-treated animals the presence of cell-free plasma haemoglobin, (approximately 25% of total haemoglobin) strengthened the diffusive component of oxygen transport, thereby preserving tissue viability.

In summary, in dogs subjected to acute haemorrhage, low-volume resuscitation with Hemoglobin glutamer-200 (bovine) 10 ml kg^{-1} was inadequate to restore cardiac output and oxygen delivery but was as effective as isovolaemic whole-blood resuscitation (32 ml kg^{-1}) in returning splanchnic blood flow and acid–base status to the pre-haemorrhage levels. These results indicate that bovine haemoglobin-based oxygen carriers (i) may not impair splanchnic perfusion in spite of their systemically vasoconstrictive action and their ability to compromise cardiac output, and (ii) may improve capillary oxygen transport efficiency and hence oxygen uptake into tissues sufficiently to allow aerobic cell metabolism to be maintained even in situations of moderately reduced arterial oxygen content.

References

1 Schlichtig R, Kramer DJ, Pinsky MR. Flow redistribution during progressive hemorrhage is a determinant of critical O_2 delivery. *J Appl Physiol* 1991; **70**: 169–78

2 Schoenberg MH, Lunberg C, Gerdin B, Smedegård G, Messmer K, Arfors KE. Hemorrhagic shock in the dog. II. Studies on central hemodynamics and regional blood flow. *Res Exp Med* 1985; **185**: 469–82

3 Fink MP. Gastrointestinal mucosal injury in experimental models of shock, trauma, and sepsis. *Crit Care Med* 1991; **19**: 627–41

4 Fiddian-Green RG, Haglund U, Gutierrez G, Shoemaker WC. Goals for resuscitation of shock. *Crit Care Med* 1993; **21** (2 Suppl.): S25–31

5 Pastores SM, Katz DP, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastro* 1996; **91**: 1697–710

6 Light RW, Jacobs EE, Rentko VT, Gawryl MS, Hughes GS. Use of HBOC-201 as oxygen therapeutic in the preclinical and clinical settings. In: Rudolph AS, Rabinovici R, Feuerstein GZ, eds. *Red Blood Cell Substitutes*. New York: Marcel Dekker, 1998; 421–36

7 Mallik A, Bodenham AR. Modified haemoglobins as oxygen transporting blood substitutes. *Br J Hosp Med* 1996; **55**: 443–8

8 Spahn DR, Leone BJ, Reves JG, Pasch T. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of non-oxygen-carrying and oxygen-carrying solutions. *Anesth Analg* 1994; **78**: 1000–21

9 Winslow RM. New transfusion strategies: red cell substitutes. *Annu Rev Med* 1999; **50**: 337–53

10 Loeb A, McIntosh LJ, Raj NR, Longnecker D. Regional vascular effects of rHb1.1, a hemoglobin-based oxygen carrier. *J Cardiovasc Pharmacol* 1997; **30**: 703–10

11 Noone RB, Mythen MG, Vaslef SN. Effect of $\alpha\alpha$-cross-linked hemoglobin and pyridoxalated hemoglobin polyoxyethylene conjugate solutions on gastrointestinal regional perfusion in hemorrhagic shock. *J Trauma* 1998; **45**: 457–69

12 Ulatowski JA, Nishikawa T, Matheson-Urbaitis B, Bucci E, Traystman RJ, Koehler RC. Regional blood flow alterations

after bovine fumaryl beta beta-crosslinked hemoglobin transfusion and nitric oxide synthase inhibition. *Crit Care Med* 1996; **24**: 558–65

13 Frankel HL, Nguyen HB, Sheadonohue T, Alton LA, Ratigan J, Malcolm DS. Diaspirin crosslinked hemoglobin is efficacious in gut resuscitation as measured by a GI tract optode. *J Trauma* 1996; **40**: 231–40

14 Ning J, Peterson LM, Anderson PJ, Biro GP. Systemic hemodynamic and renal effects of unmodified human SFHS in dogs. *Biomater Artif Cells Immobilization Biotechnol* 1992; **20**: 723–7

15 Van Iterson M, Sinaasappel M, Burhop K, Trouwborst A, Ince C. Low-volume resuscitation with a hemoglobin-based oxygen carrier after hemorrhage improves gut microvascular oxygenation in swine. *J Lab Clin Med* 1998; **132**: 421–31

16 Food and Drug Administration. 21CFR522.1125 Hemoglobin glutamer-200 (bovine). *63 Federal Register 11598*, March 10, 1998

17 Horn EP, Standl T, Wilhelm S, *et al.* Bovine hemoglobin increases skeletal muscle oxygenation during 95% of artificial arterial stenoses. *Surgery* 1997; **121**: 411–8

18 Hughes GS, Antal EJ, Locker PK, *et al.* Physiology and pharmacokinetics of a novel hemoglobin-based oxygen carrier in humans. *Crit Care Med* 1996; **24**: 756–64

19 Krieter H, Hagen G, Waschke KF, *et al.* Isovolemic hemodilution with a bovine hemoglobin-based oxygen carrier: effects on hemodynamics and oxygen transport in comparison with nonoxygen-carrying volume substitute. *J Cardiothorac Vasc Anesth* 1997; **11**: 3–9

20 Ilkiw JE. Balanced anesthetic techniques in dogs and cats. *Clin Tech Small Anim Pract* 1999; **14**: 27–33

21 Jahr JS, Lurie F, Driessen B, *et al.* An ultrapurified polymerized, hemoglobin-based oxygen carrier (HBOC): validation of the oxygen saturation measurements from the i-STAT portable clinical analyzer, Nova Co-oximeter and a blood gas analyzer in a canine model. *Clin Lab Sci* 2000; **13**: 210–21

22 Steffey EP. Inhalation anesthetics. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. *Lumb and Jones' Veterinary Anesthesia*, edn 3. Baltimore (MD): Williams & Wilkins, 1996; 297–329

23 Egan TD, Kuramkote S, Gong G, *et al.* Fentanyl pharmacokinetics in hemorrhagic shock. *Anesthesiology* 1999; **91**: 156–66

24 Dellenback RJ, Usami S, Chien S, *et al.* Effects of splenectomy on blood picture, blood volume, and plasma proteins in beagles. *Am J Physiol* 1969; **217**: 891–7

25 Wiggers HC, Ingraham RC, Dille J. Hemorrhagic-hypotension shock in locally anesthetized dogs. *Am J Physiol* 1945; **143**: 126–33

26 Haskins SC, Patz JD. Ketamine in hypovolemic dogs. *Crit Care Med* 1990; **18**: 625–9

27 Sturm JA, Wisner DH. Fluid resuscitation of hypovolemia. *Intensive Care Med* 1985; **11**: 227–30

28 Doi R, Inoue K, Kogire M, *et al.* Effects of synthetic kassinin on splanchnic circulation and exocrine pancreas in dogs. *Peptides* 1988; **9**: 1055–8

29 Li KCP, Wright GA, Pelc LR, *et al.* Oxygen saturation of blood in the superior mesenteric vein: in vivo verification of MR imaging measurements in a canine model. *Radiology* 1995; **194**: 321–5

30 Slater GI, Vladeck BC, Bassin R, Kark AE, Shoemaker WC. Sequential changes in distribution of cardiac output in hemorrhagic shock. *Surgery* 1975; **5**: 714–22

31 Kasper SM, Walter M, Grüne F, Bischoff A, Erasmi H, Buzello W. Effects of a hemoglobin-based oxygen carrier (HBOC-201) on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. *Anesth Analg* 1996; **83**: 921–7

32 Gulati A, Sharma AC, Burhop KE. Effect of stroma-free hemoglobin and diaspirin cross-linked hemoglobin on the regional and systemic hemodynamics. *Life Sci* 1994; **55**: 827–37

33 Haglund U, Abe T, Ahren C, Braide I, Lundgren O. The intestinal mucosal lesions in shock. II. The relationship between the mucosal lesions and the cardiovascular derangement following regional shock. *Eur Surg Res* 1976; **8**: 448–60

34 Bosman RJ, Minten J, Lu HR, Van Aken H, Flameng W. Free polymerized hemoglobin versus hydroxyethyl starch in resuscitation of hypovolemic dogs. *Anesth Analg* 1992; **75**: 811–7

35 Lipfert B, Standl T, Düllmann J, Helmchen U, Schulte am Esch J, Lorke DE. Histology and ultrastructure of liver and kidney following blood exchange with ultrapurified, polymerized bovine hemoglobin in comparison with hydroxyethyl starch. *Lab Invest* 1999; **79**: 573–82

36 Federspiel WJ. Popel AS. A theoretical analysis of the effect of the particulate nature of blood on oxygen release in capillaries. *Microvasc Res* 1986; **32**: 164–89

37 Page TC, Light WR, McKay CB, Hellums JD. Oxygen transport by erythrocyte/hemoglobin solution mixtures in an *in vitro* capillary as a model of hemoglobin-based oxygen carrier performance. *Microvasc Res* 1998; **55**: 54–64

38 Vandegriff KD, Olson JS. Morphological and physiological factors affecting oxygen uptake and release by red blood cells. *J Biol Chem* 1984; **259**: 12619–27

39 Rentko VT. Red blood cell substitutes. *Transfusion Med* 1992; 4: 647–51

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Tissue/blood and tissue/water partition coefficients for propofol in sheep[†,‡]

B. M. Q. Weaver[1 4]*, G. E. Staddon[2 5] and W. W. Mapleson[3]

[1]The Veterinary School, University of Bristol, Langford, Bristol BS18 7DU, UK. [2]Department of Medical Physics and Bioengineering, Bristol General Hospital, Bristol BS1 6SY, UK. [3]Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF14 4XN, UK

[4]Present address: 79 Sandford Road, Winscombe, North Somerset BS25 1JJ, UK

[5]Present address: 17 Shaldon Road, Horfield, Bristol BS7 9NN, UK

**Corresponding author*

The primary objective of this study was to determine *in vivo* tissue/blood partition coefficients of propofol for use in physiological modelling of its pharmacokinetics. The sheep was used as an animal model. In the main series of experiments, crossbred ewes received a bolus of propofol 1% (Diprivan) followed by an infusion during which blood concentrations were measured at intervals. After 2 h, the sheep were killed with an injection of potassium chloride, and tissue samples were taken for storage at –20°C and subsequent analysis. Tissue/blood partition coefficients depend on the amount of triglyceride which accumulates in blood from the propofol vehicle; for blood, free of added triglyceride, the following coefficients were calculated: brain, 3.23; heart, 5.94; kidney, 2.46; spleen, 1.86; semimembranosus muscle, ≥1.61; triceps muscle, ≥1.47. Calculated tissue/water coefficients were 35 times greater. There was indirect evidence of extraction of propofol by the lungs.

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Physiological, as opposed to empirical, modelling of pharmacokinetics allows prediction of how blood and tissue concentrations of an anaesthetic will change with time in various circumstances but, for this purpose, it is necessary to know how the agent is distributed between the various tissues and organs of the body. Little information is available on this topic with regard to propofol and so, initially, the distribution of propofol within the blood of sheep was studied.[1] The present study was carried out (under UK Home Office licences PPL 30/00861 and PIL 30/01083) to determine the uptake of propofol from the blood into the major tissues of the body and to calculate the *in vivo* tissue/blood partition coefficients.

Materials and methods

General plan

Two groups of healthy, adult, crossbred ewes were studied. In group T (six ewes) the objective was to determine tissue concentrations a few minutes after a large bolus dose of propofol. In group P (14 ewes) the objective was to determine tissue/blood partition coefficients. This was done by infusing propofol for 2 h on the assumption that, at the end of the infusion, at least the well-perfused tissues would be nearly in equilibrium with the arterial concentration. Therefore, as well as taking tissue samples, we took blood samples during the infusion to track blood concentration and to determine the arterial concentration at the time of cardiac arrest. All concentration measurements were corrected for loss in storage: the rate of loss from blood samples had

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[†] A provisional analysis of loss of propofol from tissue samples was presented to the Anaesthetic Research Society Meeting, Dundee, July 1998 (*Br J Anaesth* 1998; **81**: 630–1).

[‡] *Declaration of interest*: The *in vivo* work for this study was carried out in the Wellcome Comparative Anaesthetic Laboratory, which was provided by the Wellcome Trust. Financial support was provided by the Perry Foundation and the propofol was generously supplied by Imperial Chemical Industries Limited (now Astra-Zeneca).

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Table 1 Summary of the general plan of the investigation

Group T (tissue concentrations) (n=6, 31–57 kg)		**Group P (partition coefficients)**			
		Subgroup Pa (n=8, 35–66 kg)		**Subgroup Pb (n=6, 68–86 kg)**	
Time	**Action**	**Time**	**Action**	**Time**	**Action**
			Inhalation anaesthesia (after bolus of thiopental in four ewes) Cannulate an artery		
0 min	Propofol: bolus 10 mg kg^{-1}	0 min	Propofol: bolus 3 mg kg^{-1}; start infusion 1 ml min^{-1}	0 min	Propofol: bolus 6 mg kg^{-1}; start infusion 1 ml min^{-1} (two ewes) 2 ml min^{-1} (four ewes)
			Plus halothane or isoflurane as required		Plus isoflurane as required
		1–120 min	Arterial and venous samples	1–120 min	Venous samples
				110–140 min	Cannulate artery
				+0–12 min	Arterial and venous samples
2–7 min	Inject KCl	121–129 min	Inject KCl	123–152 min	Inject KCl
+0–30 min	Tissue samples	+10–40 min	Tissue samples	+10–40 min	Tissue samples
6–26 months	Analyse on 3–5 occasions	1–330 days	Analyse on 2–3 occasions	9–106 days	Analyse once

already been determined,[2] and the rate of loss from the tissue samples was estimated by repeat analyses over a period of time. The tissues sampled were brain, heart, kidney, liver, lungs, spleen and muscle [semimembranosus in all sheep, plus triceps in the partition-coefficient sheep (group P)]. The preparation of propofol used was 1% Diprivan.

Procedure

Caveat

This was an exploratory study so the procedure developed as the investigation progressed, as is evident from the summary in Table 1, where group P has been divided into subgroup Pa, in which arterial cannulation was performed before the propofol was started, and subgroup Pb, in which it was performed during the infusion.

Cannulation

In group T, the propofol was injected through a flexible cannula, previously placed into a jugular vein under local anaesthesia.[3] In group P, both jugular veins were similarly cannulated, ensuring that the tip of each cannula remained within the cervical region. Propofol was administered through one cannula and venous samples were drawn through the other. An artery was cannulated under general anaesthesia: a digital artery in the first four ewes in subgroup Pa, and a carotid artery in the remaining four and in all six ewes in subgroup Pb.

Euthanasia

In all groups, euthanasia was performed while the animal was still deeply anaesthetized: an intravenous injection of a saturated solution of potassium chloride at the appropriate time (Table 1) rapidly induced cardiac arrest. Within 40 min, the requisite tissue samples were removed, sealed in plastic bags and stored in a freezer at –20°C for subsequent analysis for propofol content.

Group T

A bolus of propofol 10 mg kg^{-1} induced anaesthesia and ensured that the animals were deeply anaesthetized when, 2–7 min later, the potassium chloride was injected. The tissue samples were analysed on three to five occasions between 6 and 26 months post mortem.

Subgroup Pa

In order to obtain arterial samples throughout the infusion, cannulation was performed under an alternative form of anaesthesia before any propofol was administered. Induction was with thiopental in four animals, halothane in three and isoflurane in one; in each sheep, maintenance was with the same volatile agent, or with isoflurane in the sheep with thiopental induction. Once each animal was anaesthetized, its trachea was intubated with a cuffed tracheal tube which was connected to a circle-absorber breathing system, supplied with about 300 ml min^{-1} of oxygen and incorporating an in-circle vaporizer. As soon as the cannulations were complete, a bolus of propofol 3 mg kg^{-1} was administered, followed by an infusion of the agent at 1 ml min^{-1} for 2 h. The in-circle vaporizer was used to add the same volatile agent as before the propofol, at concentrations required to ensure adequate anaesthesia, as judged clinically, throughout the procedure. Paired sampling of arterial and venous blood was scheduled for 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min after the start of the propofol infusion. Euthanasia followed while the infusion continued. Tissue samples were analysed on two or three occasions between 1 and 330 days post mortem; blood samples were analysed once between 1 and 31 days.

Subgroup Pb

Here it was realized that it would be sufficient to obtain arterial samples during only the later part of the infusion; therefore the arterial cannulation was performed after inducing anaesthesia with a larger bolus of propofol 6 mg kg^{-1} followed by the 2-h infusion. In the first two ewes, the rate of infusion was 1 ml min^{-1}, as in subgroup Pa; in the last four, the rate was 2 ml min^{-1} to provide additional information on propofol kinetics. As soon as possible after commencing the infusion, the trachea of each animal was intubated and connected to the circle breathing system. In all six sheep, the propofol was supplemented with isoflurane, from the in-circle vaporizer, according to the criterion used for subgroup Pa. Venous sampling was as in subgroup Pa; in addition three to six paired arterial and venous samples were taken in the last 10 min before cardiac arrest was induced at 123–152 min. Tissue samples were analysed once only, 9–106 days post mortem; blood samples were analysed once at 3–50 days.

Liver samples

In all but the first of the 14 ewes in group P, two samples of liver were taken. The 'early' sample was taken as soon as possible after cardiac arrest and placed in the freezer within 10–20 min of the arrest; the second, 'standard' sample was taken to the freezer 10–25 min later, along with the samples of the other tissues. This was done to provide information on possible loss by continuing metabolism of propofol in the liver before freezing.

Analysis of propofol in blood and tissue

Analysis of propofol in blood samples was as described previously[2] with derivatizations[4] of two 1-ml subsamples, each analysed in duplicate. For analysis of propofol in tissue, a subsample of each frozen tissue sample was taken by grating and the remainder returned to the freezer. The grated subsample was chopped, and further broken down with a pestle and mortar to facilitate homogenization. It was then weighed and potassium dihydrogen phosphate (0.1 M) was added to produce a 1:2 w/v suspension. This was homogenized in a liquidizer, with only short bursts of activity to avoid heating, which would have denatured the tissue. Each subsample was then treated in the same way as the blood samples, each derivatization using 1.5 ml of homogenate.

Data processing

Processing was commenced only when all the data had been collected; a detailed account is given in Appendix 1. Analysis of variance was used to determine the best way of summarizing the loss rates from tissue samples. The resulting rates were used to estimate the concentration in each tissue sample at day 0, i.e. the day of sampling. Concentrations in liver samples were additionally corrected for metabolic loss before freezing. Regression analysis was used to estimate the arterial concentration at the time of cardiac arrest in each sheep—directly in subgroup Pa, but in subgroup Pb a mean arterial–venous difference was added to the fitted venous concentration. Partition coefficients were obtained by dividing each day-0 tissue concentration by the corresponding arterial concentration at cardiac arrest. $P<0.05$ was regarded as significant.

Results

Loss from tissue samples during storage at –20°C

The data analyses in Appendix 1 showed that the loss from tissue samples was better represented by a linear decrease in log concentration rather than in actual concentration, implying an exponential decay of propofol content. It also emerged that separate slopes were needed for loss after a bolus (group T) and after an infusion (group P), and for loss from spleen and non-spleen tissues after a bolus (Table 2). Only non-spleen tissue after a bolus showed a significant loss rate (the confidence limits excluded zero). The rates for spleen, and for all tissues after an infusion, were small and non-significant; they were assumed to be zero for calculating the day-0 concentrations.

Table 2 Loss of propofol from tissue samples stored at –20°C. Concentration in μg g^{-1}. CL=95% confidence limits; *data from subgroup Pa, assumed to apply to whole of group P

Method of administration	**Rate of change of concentration**				**Half-life (yr)**
	Log$_{10}$(concentration) per day		**% per day, compound**		
	Estimate	SE	**Estimate**	**CL**	
Bolus (group T)					
Non-spleen	–0.001 111	0.000 121	–0.255	–0.31,–0.20	0·74
Spleen	0.000 212	0.000 197	0.049	–0.04, 0.14	–3·9
Infusion (1 ml min^{-1}) (group P)*					
All tissues	–0.000 047	0.000 153	–0.011	–0.08, 0.06	18

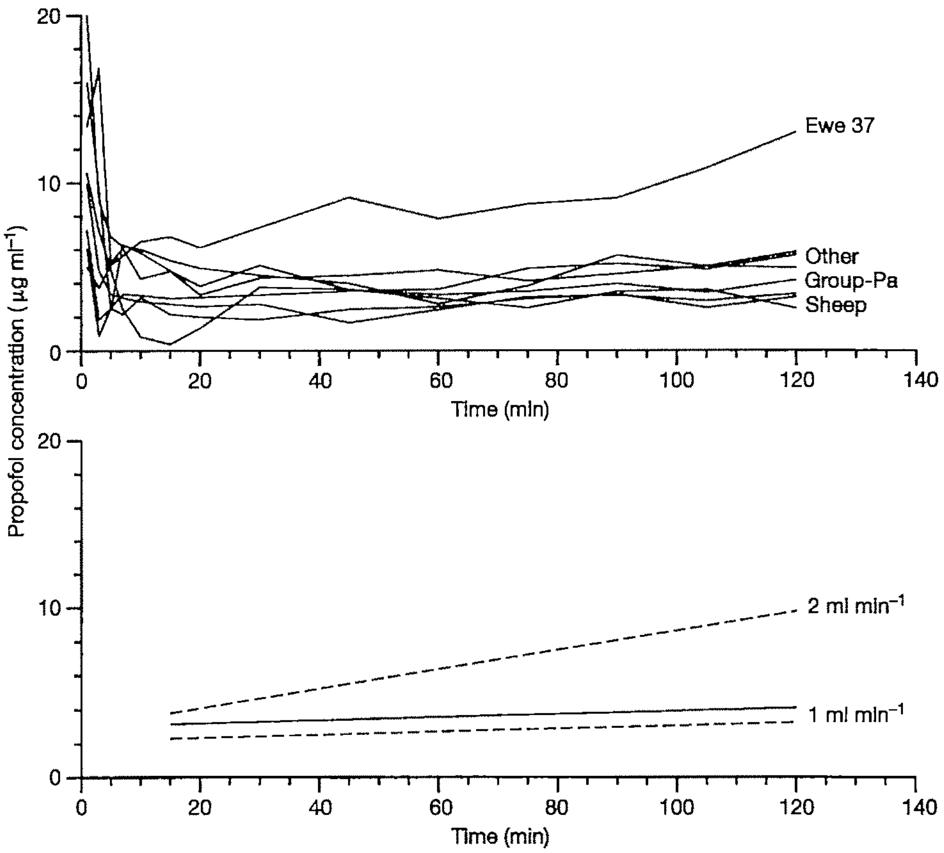

Fig 1 Concentrations of propofol in blood, corrected for loss in storage, plotted against time. Top: arterial concentrations in individual sheep of subgroup Pa, infused at 1 ml min^{-1}. Bottom: mean of regression lines fitted (from 15 min onwards) to arterial (continuous line) and venous (broken lines) concentrations in each sheep of subgroup Pa, infused at 1 ml min^{-1}, and to venous concentrations in each of those subgroup Pb sheep infused at 2 ml min^{-1}. The slopes of the fitted lines are [mean (SE)]: for subgroup Pa sheep infused at 1 ml min^{-1} (n=7, i.e. excluding ewe 37) 0.55 (0.21) and 0.55 (0.25) µg ml^{-1} h^{-1} for arterial and venous concentrations respectively; and, for subgroup Pb sheep infused at 2 ml min^{-1} (n=4, venous concentrations only), 3.4 (0.70) µg ml^{-1} h^{-1}. The corresponding residual standard deviations were 0.72, 0.65 and 1.54 µg ml^{-1}.

Loss from liver samples before storage at –20°C

The mean rate of change of $\log_{10}$(concentration in µg g^{-1}) between the early and standard samples was –0.0134 min^{-1} (SE 0.0037), or 3% min^{-1} compound (95% confidence limits 1.2, 4.8% min^{-1}).

Tissue concentrations

Estimated concentrations at the time of cardiac arrest are listed in Table 3 for each tissue and for each method of administration. The estimates are in terms of geometric mean with asymmetrical confidence limits. Estimates for liver are after correcting for loss before freezing.

Blood concentrations

In subgroup Pa sheep, infused at 1 ml min^{-1}, arterial concentrations generally increased slowly after the transient produced by the initial bolus, but relatively rapidly in ewe 37 (Fig. 1, top). However, to maintain deep anaesthesia, inhalation supplementation was required in all cases (including ewe 37) after an average of 10 min. When propofol was infused at 2 ml min^{-1}, the venous concentrations (the only ones measured until near the end of the infusions in subgroup Pb) were greater than those at 1 ml min^{-1} (Fig. 1, bottom) and increased much more rapidly. Despite this, supplementation with an inhalational agent was required in the 2 ml min^{-1} infusions after approximately 1 h.

Partition coefficients

From this point onwards the appropriate split of the group P sheep is not into the procedure-based subgroups Pa and Pb, but according to the two rates of infusion: 10 sheep at 1 ml min^{-1} and four at 2 ml min^{-1}. Corresponding partition coefficients for each tissue, for each infusion rate, are listed in terms of geometric mean and asymmetrical confidence limits in Table 4. It should be noted that, although many tissue concentrations in the 2 ml min^{-1} sheep were nearly double those in the 1 ml min^{-1} sheep (Table 3), the arterial concentrations after 2 h were more than double (Fig. 1, bottom), so the partition coefficients are systematically, and significantly (P<0.001), somewhat smaller in the 2 ml min^{-1} sheep.

Table 3 Tissue concentrations of propofol ($\mu g\ g^{-1}$) in each tissue for each method of administration, geometric mean (95% confidence limits); ratios of the means for the two rates of infusion; pooled SD of $\log_{10}$(concentration in $\mu g\ g^{-1}$); perfusion of each tissue derived from Pearson.[5] concn=concentration; Semimem=semimembranosus; *pooled between the two infusion rates only; the SD of $\log_{10}$(concentration) for muscle in the bolus group was 0.585

Tissue	Tissue concentration of propofol ($\mu g\ g^{-1}$)				Pooled SD of $\log_{10}$(concn)	Tissue perfusion (ml min^{-1} g^{-1})
	Bolus only (n=6) (mean mass 41.1 kg)	Infusion 1 ml min^{-1} (n=10) (mean mass 52.2 kg) (mean rate 11.5 mg kg^{-1} h^{-1})	Infusion 2 ml min^{-1} (n=4) (mean mass 76.0 kg) (mean rate 15.8 mg kg^{-1} h^{-1})	Ratio (2/1)		
Brain	65.3 (48.6, 87.7)	11.0 (8.8, 13.9)	20.3 (14.1, 29.2)	1.84	0.149	0.69
Heart	66.5 (49.5, 89.3)	20.5 (16.3, 25.8)	35.1 (24.4, 50.3)	1.71	0.149	0.45
Kidney	44.6 (31.2, 63.7)	8.4 (6.4, 11.0)	14.8 (9.6, 22.9)	1.77	0.179	2.10
Liver	35.0 (14.8, 83.0)	5.0 (2.6, 9.8)	9.5 (3.3, 27.2)	1.88	0.435	0.131
Lungs	2.0 (0.6, 7.0)	0.9 (0.4, 2.3)	0.2 (0.05, 0.8)	0.22	0.576	16.2
Spleen	13.3 (8.6, 20.5)	6.3 (4.5, 8.9)	10.8 (6.3, 18.3)	1.70	0.219	0.137
Semimem	7.6 (1.8, 31.0)	6.3 (4.6, 8.7)	6.7 (4.0, 11.1)	1.06	0.204*	0.022
Triceps	–	5.3 (4.0, 7.2)	7.3 (4.6, 11.7)	1.37	0.188*	0.022

Table 4 Raw tissue/blood partition coefficients (λ) for each tissue for each infusion rate, geometric mean (95% confidence limits); ratios of the two means for each tissue; pooled standard deviation of $\log_{10}(\lambda)$; tissue densities. Tissue densities, used to convert tissue concentrations from $\mu g\ g^{-1}$ to $\mu g\ ml^{-1}$, are means (SDs) of those for 2–7 mammalian species other than sheep[6] because no values could be traced for this species. Semimem=semimembranosus. Coefficients for the muscles should be regarded as lower limits (see Discussion)

Tissue	Tissue/blood partition coefficients			Pooled SD of $\log_{10}(\lambda)$	Tissue density used (g ml^{-1}): mean (SD)
	1 ml min^{-1} (n=10) (mean 11.5 mg kg^{-1} h^{-1})	2 ml min^{-1} (n=4) (mean 15.8 mg kg^{-1} h^{-1})	Ratio (2/1)		
Brain	2.39 (1.97, 2.91)	1.83 (1.35, 2.49)	0.77	0.122	1.041 (0.004)
Heart	4.50 (3.54, 5.73)	3.19 (2.18, 4.68)	0.71	0.152	1.051 (0.012)
Kidney	1.85 (1.33, 2.55)	1.36 (0.81, 2.26)	0.73	0.204	1.055 (0.006)
Liver	1.13 (0.56, 2.29)	0.88 (0.29, 2.70)	0.78	0.446	1.076 (0.007)
Lungs	0.21 (0.08, 0.53)	0.02 (0.004, 0.08)	0.09	0.591	1.042 (0.013)
Spleen	1.41 (1.02, 1.94)	1.00 (0.60, 1.65)	0.71	0.203	1.066 (0.007)
Semimem	1.40 (1.05, 1.87)	0.62 (0.39, 0.98)	0.44	0.184	1.065 (0.010)
Triceps	1.19 (0.93, 1.51)	0.68 (0.46, 0.99)	0.57	0.152	1.065 (0.010)
Mean of well-perfused tissues, excluding liver and lungs			0.73		

Table 5 Residual plasma mass in sheep tissues as percentage of blood-free tissue mass.[5] *Estimated from an equation[5] relating plasma and spleen packed-cell fractions to the sequestration of red cells in spleen, and using measurements of the decrease of packed-cell fractions in the first minute after a bolus of propofol in group P and in other[1] sheep

Tissue	Residual plasma (%)
Muscle	1.0
Brain	1.0
Heart	2.3
Spleen (contracted)	3.9
Kidney	3.9
Liver	6.2
Lung	20
Spleen (max engorged)	250
Spleen (1 min after a bolus of propofol)*	100

Discussion

Tissue storage

The pattern of loss of propofol from tissues during storage (Table 2) is surprising: substantial loss from non-spleen bolus tissues, but small and non-significant changes in the remainder. It does not seem possible to attribute the pattern to experimental errors because the methods of storage and analysis were the same throughout the study, and the analyses of bolus and infusion tissues overlapped in time. Propofol is known to evaporate but its boiling point is 242.3°C (J. B. Glen, personal communication) and, even if evaporation were the method of loss in storage, half-life should be proportional to the solubility of propofol in the tissues; yet there was nothing exceptional about spleen in terms of partition coefficient (Table 4).

Another possibility is degradation of propofol. Some evidence can be adduced that the distribution of the propofol *vehicle* may match the pattern of loss in Table 2. An earlier paper[3] noted that the vehicle is very similar to Intralipid: a major component of both is soya bean oil. For convenience, the vehicle will be referred to below as 'intralipid', with a lower-case 'i'. The earlier paper[3] reported plasma concentrations of triglyceride. Those concentrations arose from measurements in some of the present sheep and in other crossbred ewes subjected to similar boluses and infusions of

Table 6 Tissue/water partition coefficients as geometric mean (95% confidence limits) derived by multiplying each tissue/blood coefficient by the estimated blood/water partition coefficient applicable at the time of cardiac arrest in each sheep (Appendix 2, equations 16, 17); coefficients for the partitioning between tissues and normal sheep blood derived by dividing each tissue/water coefficient by the blood/water coefficient for normal blood (35.03, Appendix 2, equation 13); pooled standard deviation of $\log_{10}(\lambda)$. λ=partition coefficient (tissue/water or tissue/normal-blood). Values apply to both infusion rates; coefficients for the muscles should be regarded as lower limits (see Discussion)

Tissue	Partition coefficients (λ)		Pooled SD $\log_{10}(\lambda)$
	Tissue/water	Tissue/normal-blood	
Brain	113.2 (97.1, 132.0)	3.23 (2.77, 3.77)	0.115
Heart	208.2 (170.3, 254.4)	5.94 (4.86, 7.26)	0.150
Kidney	86.2 (65.2, 114.0)	2.46 (1.86, 3.25)	0.208
Liver	53.6 (29.0, 99.1)	1.53 (0.83, 2.83)	0.458
Lungs	5.3 (2.4, 11.6)	0.15 (0.07, 0.33)	0.587
Spleen	65.1 (50.1, 84.5)	1.86 (1.43, 2.41)	0.195
Semimembranosus	56.5 (44.1, 72.4)	1.61 (1.26, 2.07)	0.185
Triceps	51.6 (42.3, 62.9)	1.47 (1.21, 1.80)	0.148

propofol. The initial increases in plasma concentration shortly after the injection of a bolus of propofol were sufficient to account for all the injected intralipid. Therefore, the amount of intralipid in each tissue would depend only on the amount of plasma it contained. Again there is nothing exceptional about the spleen when it is contracted but, when maximally engorged it contains about 12 times as much plasma as any other tissue (Table 5), and five times as much at the degree of engorgement estimated for the present studies after a bolus of propofol (Table 5). This implies that, in group T, the spleen contained five times as much intralipid as any other tissue.

At the end of a 2-h infusion, the plasma triglyceride concentrations had increased greatly[3] but accounted for only half the total amount injected in the infusions. This is consistent with tissue samples in the infusion studies containing substantial amounts of at least some components of intralipid. Therefore perhaps the pattern of loss rates in Table 2 can be attributed to some component of intralipid having a preservative action on propofol.

This hypothesis is clearly speculative but, when these findings on loss rate were presented to the Anaesthetic Research Society,[7] none of the alternative hypotheses elicited from the members was consistent with all the observations.

The loss rate from liver during storage at –20°C was no different from that for other non-spleen tissues. Therefore, there was no liver-specific metabolism once the samples were frozen.

Tissue distribution

There is no ready means of knowing whether the concentrations for the bolus-only method (Table 3) were before, at or after the postinjection peak, except that the huge perfusion of the lung will ensure that the measured concentration relates to well after its first-pass peak. However, the concentrations were generally greater for the well-perfused tissues than for muscle and the concentrations in the former were greater than the corresponding concentrations in the infusion experiments.

After a 2-h infusion, well-perfused tissues should all be nearly in equilibrium with the arterial concentration at the time of cardiac arrest. The highest concentration was then found in the heart and was about double that in any other tissue. The smallest concentration was found in the lungs, where 'extraction' of propofol has been reported in sheep;[8] but the concentration in liver, where metabolism is known to occur, was comparable to that in other tissues (Table 3). Perhaps there was an even greater loss from lung tissue before freezing. Support for extraction by the lungs is possibly indicated by the pooled standard deviation for lungs (Table 3) being even greater than that for liver, and three to four times greater than for any other tissue. Further evidence of extraction by the lung may be hidden in the anomalous behaviour of ewe 37 (see below).

Partition coefficients

Raw tissue/blood coefficients

The partition coefficients in Table 4 arise from dividing all the fitted day-0 tissue concentrations (converted to $\mu g\ ml^{-1}$) for each sheep by the corresponding estimated arterial concentration at the time of cardiac arrest. The differences between tissues therefore follow the same pattern as the tissue concentrations in Table 3. The systematic differences between the two infusion rates are related to the triglycerides from the propofol vehicle, which accumulate in blood during the infusions—more so at 2 ml min^{-1} leading to smaller partition coefficients. Therefore, the coefficients in Table 4 are relevant only to the particular circumstances of those infusions.

Tissue/water and tissue/normal-blood coefficients

A set of more generally applicable tissue/*water* coefficients was derived as follows. From data previously reported[1 3] or obtained from published work,[9–11] it was found possible to derive a general equation (Appendix 2, equation 12) for the blood/water partition coefficient as a function of the triglyceride concentration in plasma and of packed-cell fraction. This was then quantified for the present study in equations 16 and 17, to give the blood/water coefficient as a function of time for each sheep. Tissue/water coefficients could then be derived by multiplying each tissue/blood coefficient by the blood/water coefficient for the end of the corresponding infusion. Unlike in Table 4, differences between the mean tissue/water partition coefficients for the two infusion rates were not significant, so overall geometric means and confidence limits were calculated. These are displayed in Table 6, together with a set of tissue/normal-blood partition coefficients. These were obtained by dividing each tissue/water coefficient by the blood/water coefficient for 'normal' sheep blood (35.0; Appendix 2, equation 13).

These tissue/normal-blood coefficients are somewhat artificial because they will be changed as soon as any propofol is administered, but they may be useful for comparison with corresponding values for other drugs: they are broadly comparable to values for inhalation anaesthetics.[12] They are mostly about 30% higher than those in Table 4 for 1 ml min^{-1}, and about twice those for 2 ml min^{-1}.

Possible systematic errors

Both sets of coefficients (Tables 4 and 6) are susceptible to systematic errors arising from incomplete equilibration between tissue and blood. A cup-and-bucket simulation method was devised for correcting for this (details are available from the authors). It was applied to each individual coefficient, and a geometric mean was calculated for each tissue. For the well-perfused tissues, the incompleteness was no more than 1% except for liver (4% because of one very large tissue/blood coefficient). Therefore, these coefficients would be little influenced by errors in the assumed perfusions (Table 3). Muscles showed about 20% incompleteness, but this value is somewhat uncertain because the results were then critically dependent on the perfusion assumed. Therefore, the coefficients given for muscle should be regarded simply as lower limits. In addition, the coefficients for liver and lungs will always be low because *in vivo* metabolism and extraction[8] respectively prevent these tissues ever reaching equilibrium with blood.

There are three further sources of uncertainty in the partition coefficients. First, volatile anaesthetics can affect the binding of drugs to proteins, but for halothane and isoflurane the effect is small (0–16%) at 1 minimum alveolar concentration (MAC)[13–15] and probably smaller at the <1 MAC needed in our study to supplement the propofol infusion. Secondly, non-linearity of binding of propofol has been reported, but only for low concentrations (1%) of human serum albumin and haemoglobin and not for human plasma.[16] In the present study, despite the nearly twofold differences in mean tissue concentrations between the two infusion rates (Table 3) the corresponding differences in mean tissue/water coefficients were not significant and no more than 14% for the non-metabolizing, well-perfused tissues (brain, heart, kidney, spleen). This suggests little non-linearity in the present circumstances. Finally, we estimate that uncertainties in some of the parameters used in Appendix 2, taken from earlier work,[1] might change the tissue/water coefficients by ±20% and the tissue/normal blood coefficients by ±10%.

Other sources of partition coefficients

Ludbrook and colleagues[17] give a plot of calculated brain concentrations of propofol in sheep against measured sagittal-sinus concentration during and after a 45-min infusion of 1 ml min^{-1} of propofol. The slope of the plot corresponds to a brain/blood partition coefficient of about 3.5. This is comparable to our estimates of 3.2 (Table 6) for before any propofol and 2.4 for the end of a 2-h infusion of 1 ml min^{-1} (Table 4). Brain/blood concentration ratios of 3.5 and 2.9 have been found[18] for propofol in the rat after 15- and 30-min infusions respectively. Perhaps this decrease with duration of the infusion reflects increasing lipid accumulation in the blood.

The anomalous ewe 37

In this sheep the arterial concentration increased unusually rapidly (Fig. 1, top). This was not associated with an unusually steep increase in plasma triglyceride concentration (ewe 37 was one of those in which triglyceride concentrations were measured).[3] In addition, for every tissue in ewe 37, the propofol concentration was greater than in any other sheep: as much as eight times greater than the next largest for lung. On the other hand, each partition coefficient for ewe 37 was within, or almost within, the corresponding range of values for other sheep infused at 1 ml min^{-1}, except for lung, where the coefficient for ewe 37 was three times the next largest, reaching a value of 0.95. This approaches the mean coefficients in Table 4 for many other tissues. This pattern of results suggests that extraction by the lungs was much less in ewe 37 than in the other sheep. It is consistent with the finding that extraction by the lungs was very variable between sheep.[8]

Possible mechanisms of extraction by the lungs

It seems very unlikely that this extraction is a result of elimination of propofol vapour in the expired gas because of the high boiling point of propofol (242.3°C) (J. B. Glen, personal communication). The alternative of some enzymatic transformation of propofol to a substance not detected by our analysis method, with a near absence of the necessary enzyme in ewe 37, seems more plausible. The non-linear nature of the extraction process[19] also points to an enzyme, not evaporation. The presence of an enzyme in the lungs would be 'logical' if it converted the propofol to a more volatile form (perhaps propane or propene, boiling points –42 and –47°C respectively), which would then be excreted in the expired gas. Although extrahepatic extraction has been reported in humans,[20 21] the only evidence of the lungs being involved is of 10–20% extraction in two of eight patients.[22] This may be an indication that enzymatic processes are less transferable between species than are partition coefficients.

Implications for target-controlled infusions of propofol

Target-controlled infusion anaesthesia aims to provide and maintain a preset blood concentration of propofol. Therefore, as the blood/water coefficient increases with increasing triglyceride concentration during an infusion, the concentration in the water phase of blood will decrease progressively; and it is this concentration with which the site of action of propofol equilibrates.

The more recently introduced 2%, and 6%,[23] preparations of propofol should lead to less accumulation of triglyceride in blood and hence to smaller blood/water and larger tissue/blood partition coefficients. This will facilitate uptake from blood to tissue, so that a given mg kg^{-1} min^{-1} infusion regimen should give smaller blood concentrations than intended but greater tissue concentrations.

In conclusion, this study provides a set of tissue/blood and tissue/water partition coefficients for propofol for some of the major organs—an essential ingredient of the physiological modelling of pharmacokinetics. The study also shows that the physiological modelling of any agent requiring a lipid carrier will be more complex than for other agents. In parallel with this, empirical models may need to be fitted to new observational data obtained when using each new formulation. The study demonstrates that, logically, target-controlled infusion should aim for a constant concentration not in whole blood but in the aqueous phase of blood.

Appendix 1

Data processing

Loss of propofol from tissue samples during storage

The investigational unit for loss at −20°C is the sample, so a separate straight line was fitted to the measurements on each standard sample in order to obtain a slope for loss rate in each sample. This was done in a single regression analysis and therefore with a single residual variance. Initially, only those samples with three or more measurements were used. This analysis showed that, with log concentration, as opposed to actual concentration, the fit was better (a straight line accounted for a larger fraction of the variance around the mean for the sample); also the residuals were then more nearly normally distributed.

A second, similar analysis used only log concentration but incorporated all samples with two or more measurements. The resulting individual slopes had large standard errors, about equal to each slope, and so required averaging. A first analysis of variance of the slopes, weighted inversely to the squares of the standard errors of the individual slopes, showed that this needed to be done separately for bolus and infusion data. In a similar weighted analysis of the bolus-only data, there was a significant difference of slope between spleen and the other tissues ($P<0.0001$), but no significant difference between the other tissues ($P=0.7$) nor between sheep ($P=0.3$). The splenic tissue showed a non-significant increase in propofol content during storage ($P=0.3$). In the infusion data, there was no significant difference between any of the tissues ($P=0.8$) nor between sheep ($P=0.8$). The loss rates are summarized in Table 2.

Estimated log concentration in each tissue sample at day 0

For each sample, the log concentration at day 0 was taken to be the intercept of a line fitted to the log measured concentrations for that sample. For non-spleen bolus tissues, the common, fitted slope was used, but for all the other samples zero slope was used. The fitting process was done separately for each tissue sample.

Correction of liver concentrations for loss before freezing

Loss rates from liver samples before freezing, obtained from measurements on the early and standard samples, were equally consistent between sheep whether expressed in terms of log concentration or actual concentration. For consistency with loss at −20°C, a mean loss rate of log concentration was calculated and assumed to apply to each liver sample during the time from cardiac arrest to the freezing of that sample. This led to a set of liver concentrations corrected to the time of cardiac arrest.

Blood concentrations

The measured concentrations were first corrected for an exponentially declining loss in storage of 0.7% per day compound.[2]

In the infusion experiments, the tissues would be at or approaching equilibrium with the arterial concentration at the time of cardiac arrest. In subgroup Pa (Fig. 1, top), the arterial concentration at cardiac arrest was estimated for each sheep by fitting a straight line to all the measurements (from 15 min onwards to avoid transients after the initial bolus) (Fig. 1, bottom) and extrapolating the line by a few minutes to the time of cardiac arrest (Table 1). In subgroup Pb, the venous concentration at cardiac arrest was similarly estimated for each sheep, and then corrected to an estimated arterial concentration by using the arteriovenous pairs of measurements in the last 12 min of each infusion.

An analysis of variance of the arterial–venous differences in subgroup Pb showed that there were no significant differences between the means for the two infusion rates used in that subgroup, but that there were significant differences between sheep. Therefore, for each sheep, the fitted venous concentration at cardiac arrest was corrected by the addition of the mean arterial–venous difference for that sheep.

Partition coefficients

The above processing provided, for each infusion sheep, the estimated concentration in each tissue at the time of sampling, and the estimated concentration in arterial blood at the time of cardiac arrest. Therefore, partition coefficients were obtained by dividing each tissue concentration by the corresponding arterial concentration. Each tissue concentration was first converted from µg g^{-1} to µg ml^{-1} by multiplying by the corresponding tissue density (Table 4).

Summarizing tissue concentrations and partition coefficients

Analysis of variance of tissue concentrations and of partition coefficients (in terms of either actual or log values) showed clear differences between tissues ($P<0.0001$) for each method of administration. Examination of the residuals showed that, after allowing for different standard deviations in different tissues, the distribution of the residuals was consistent with normality for log concentration and log partition coefficient ($P>0.2$) but not for actual concentration or partition coefficient ($P<<0.001$). Within each tissue, variances of log concentration and of log partition coefficient were sufficiently consistent to justify pooling the standard deviations of the log values between methods of administration, except that a separate, larger standard deviation was needed for muscle in the bolus group. Means and confidence limits were then calculated in terms of log values (using the pooled standard deviation) and converted to geometric means with asymmetrical limits (Table 3).

Statistical analyses

These were done with the statistical package GLIM.[24] [25] The Shapiro-Francia W′ test[26] was used to test the normality of distributions. All logarithms were to the base 10.

Appendix 2

Theory for the calculation of blood/water partition coefficients

Estimation of the concentration of triglyceride in plasma as a function of time

Let C be the concentration of triglyceride in plasma in mmol litre^{-1}. Measurements of such concentrations were made in crossbred ewes, similar to the present ones, injected with a bolus of propofol 6 mg kg^{-1} followed by a 2-h infusion of 1 or 2 ml min^{-1}.[3] The results showed that the normal, pre-bolus concentration of triglyceride was

$$C_0=0.222.$$

Subsequently the measured concentration could be well represented by an instantaneous step increase followed by a linear increase with time. For the 1 and 2 ml min^{-1} infusion rates the step increases were respectively

$$\Delta C_{bol1}=1.151$$
$$\Delta C_{bol2}=1.918.$$

The slope of the linear trend, in mmol litre^{-1} h^{-1}, could be represented by

$$dC/dt=-0.26+0.0151\times x$$

where x is the infusion rate in mg kg^{-1} h^{-1}.

Diprivan 1% contains 100 mg triglyceride (soya-bean oil)[11] per ml. Therefore, an infusion of 1 ml min^{-1} Diprivan contains $100\times60/M$ mg kg^{-1} h^{-1} triglyceride, where M is body mass in kg. Therefore, in terms of mmol litre^{-1} min^{-1},

$$dC/dt=-0.004\,33+1.51\times\dot{I}/M$$

where $\dot{I}$ is the infusion rate of propofol in ml min^{-1}.

Therefore, the total concentration of triglyceride at any time, in mmol litre^{-1}, is given by

$$C=C_0+\Delta C_{bol}+(-0.004\,33+1.51\times\dot{I}/M)\times t \qquad (1)$$

where t is time in minutes.

In fact, the step increase in the 1 ml min^{-1} sheep was much the same as in the 2 ml min^{-1} sheep (1.92 mmol litre^{-1}), but the concentration then decreased rapidly to join the line defined by equation 1. On the other hand, the step increase to be expected from the bolus of 3 mg kg^{-1} used in most of the present 1 ml min^{-1} sheep can be expected to produce a step increase of a little less than 1.15 mmol litre^{-1}, followed by a drift up to the line of equation 1. That the equation is indeed reasonably applicable to all the present sheep is shown by the fact that the tissue/water partition coefficients (Table 6), which depend on equation 1, have much the same pooled standard deviation between sheep as the raw tissue/blood coefficients (Table 4).

To convert to fractional concentration (litre litre^{-1}) of triglyceride in plasma, f_{tr}, multiply by 0.861 (mean millimolar mass, g mmol^{-1}) and divide by 877 (mean density, g litre^{-1}):[10]

$$f_{tr}=0.000\,982\times\{C_0+\Delta C_{bol}+(-0.004\,33+1.51\times\dot{I}/M)\times t\}. \qquad (2)$$

Estimation of the triglyceride/water partition coefficient, $\lambda_{tr/w}$, for propofol

Let v_x, m_x, ρ_x be the volume, mass and density respectively of component x in 1 ml of Diprivan, where x can be p=propofol, tr=triglyceride or a=aqueous phase. Also let $m_{p,x}$ and $C_{p,x}$ be the mass and mass/volume concentration respectively of propofol in phase x. Then

$$m_{p,a}=C_{p,a}\times v_a$$

where

$$v_a=1-v_{tr}-v_p.$$

Also

$$C_{p,tr}=(m_p-m_{p,a})/v_{tr}$$
$$=\{m_p-C_{p,a}\times(1-v_{tr}-v_p)\}/v_{tr}.$$

Therefore the triglyceride/water partition coefficient for propofol is given by

$$\lambda_{tr/w}=C_{p,tr}/C_{p,a}=\{m_p/C_{p,a}-(1-v_{tr}-v_p)\}/v_{tr}$$

where, using published values for m_p, m_{tr},[11] $C_{p,a}$,[9] and ρ_{tr},[10] and assuming 1 g ml^{-1} for the density of propofol (it has very little influence on the outcome),

$$m_p=10 \text{ mg}$$
$$C_{p,a}=0.018\,57 \text{ mg ml}^{-1}$$
$$v_{tr}=m_{tr}/\rho_{tr}=0.1 \text{ g}/0.877 \text{ g ml}^{-1}$$
$$v_p=m_p/\rho_p=0.01 \text{ g}/1 \text{ g ml}^{-1}.$$

Therefore

$$\lambda_{tr/w}=4715. \qquad (3)$$

Derivation of the blood/water partition coefficient of propofol, $\lambda_{b/w}$, as a function of the partition coefficients and fractional concentrations of the components of blood

Let C_n=mass/volume concentration of propofol in n, $f_{m,n}$=volume fraction of m in n (in plasma where n is omitted), and $\lambda_{m/n}$=volume/volume partition coefficient of propofol between m and n, where m and n can be b=blood, c=(red) cell, pl=plasma, pr=protein, tr=triglyceride, w=water and npl=non-protein liquid (water plus triglyceride). Then

$$\lambda_{\mathrm{pl/w}}=\frac{C_{\mathrm{pl}}}{C_{\mathrm{w}}}=\frac{f_{\mathrm{pr}}\times C_{\mathrm{pr}}+f_{\mathrm{tr}}\times C_{\mathrm{tr}}+(1-f_{\mathrm{pr}}-f_{\mathrm{tr}})\times C_{\mathrm{w}}}{C_{\mathrm{w}}}$$

which reduces to

$$\lambda_{\mathrm{pl/w}}=f_{\mathrm{pr}}\times(\lambda_{\mathrm{pr/w}}-1)+f_{\mathrm{tr}}\times(\lambda_{\mathrm{tr/w}}-1)+1. \qquad (4)$$

Also

$$\lambda_{\mathrm{b/w}}=\lambda_{\mathrm{pl/w}}\times(1-f_{\mathrm{c,b}})+\lambda_{\mathrm{c/w}}\times f_{\mathrm{c,b}}.$$

Therefore

$$\lambda_{\mathrm{b/w}}=\{f_{\mathrm{pr}}\times(\lambda_{\mathrm{pr/w}}-1)+f_{\mathrm{tr}}\times(\lambda_{\mathrm{tr/w}}-1)+1\}\times(1-f_{\mathrm{c,b}})+\lambda_{\mathrm{c/w}}\times f_{\mathrm{c,b}}. \qquad (5)$$

Quantification of the equation for the blood/water partition coefficient

In similar crossbred ewes, measurements on samples of normal blood, spiked with 5 μg propofol ml^{-1},[1] gave f_{pr}=0.0427 (76.4 g protein per litre of plasma ÷ 1.79 g protein per ml protein), $\lambda_{\mathrm{pr/npl}}$=283 and $\lambda_{\mathrm{c/pl}}$=1.42. From these data, other terms in equation 5 can be derived as follows:

$$\lambda_{\mathrm{pr/w}}=\lambda_{\mathrm{pr/npl}}\times\lambda_{\mathrm{npl/w}} \qquad (6)$$

and

$$\lambda_{\mathrm{c/w}}=\lambda_{\mathrm{c/pl}}\times\lambda_{\mathrm{pl/w}} \qquad (7)$$

where

$$\lambda_{\mathrm{npl/w}}=\frac{C_{\mathrm{npl}}}{C_{\mathrm{w}}}=\frac{f_{\mathrm{tr}}\times C_{\mathrm{tr}}+(1-f_{\mathrm{pr}}-f_{\mathrm{tr}})\times C_{\mathrm{w}}}{(1-f_{\mathrm{pr}})\times C_{\mathrm{w}}}$$

which reduces to

$$\lambda_{\mathrm{npl/w}}=\frac{f_{\mathrm{tr}}\times(\lambda_{\mathrm{tr/w}}-1)}{1-f_{\mathrm{pr}}}+1. \qquad (8)$$

The concentration of triglyceride in plasma from normal sheep has been estimated above: C_0=0.222 mmol litre^{-1}=0.191 g litre^{-1}; however, in the spiked blood,[1] the 5 μg ml^{-1} of propofol would be accompanied by 50 μg ml^{-1} (= 0.050 g litre^{-1}) of triglyceride.[11] Therefore, for the spiked blood, the concentration would be 0.191+0.050=0.241 g litre^{-1}; and, in litre litre^{-1}

$$f_{\mathrm{tr}}=0.000\,275. \qquad (9)$$

Then, using equations 9 and 3 in equation 8 gives

$$\lambda_{\mathrm{npl/w}}=\frac{0.000\,275\times4714}{1-0.0427}+1=2.35$$

and, from equation 6,

$$\lambda_{\mathrm{pr/w}}=283\times2.35=666. \qquad (10)$$

Therefore, *in the spiked blood*, using equations 10, 9 and 3 in equation 4,

$$\lambda_{\mathrm{pl/w}}=0.0427\times665+0.000\,275\times4714+1=30.69.$$

Then equation 7 leads to the generally applicable cell/water partition coefficient,

$$\lambda_{\mathrm{c/w}}=1.42\times30.69=43.58. \qquad (11)$$

Substituting equations 10, 3 and 11 in equation 5 gives

$$\lambda_{\mathrm{b/w}}=(0.0427\times665+f_{\mathrm{tr}}\times4714+1)\times(1-f_{\mathrm{c,b}})+43.58\times f_{\mathrm{c,b}}$$
$$=(29.40+4714\times f_{\mathrm{tr}})\times(1-f_{\mathrm{c,b}})+43.58\times f_{\mathrm{c,b}}. \qquad (12)$$

For *normal (unspiked) sheep blood*, equation 2 reduces to

$$f_{\mathrm{tr}}=0.000\,982\times C_0=0.000\,218$$

and[5]

$$f_{\mathrm{c,b}}=0.35$$

whence equation 12 becomes

$$\lambda_{\mathrm{b/w}}=30.42\times(1-0.35)+43.58\times0.35=35.03. \qquad (13)$$

During the infusions, the pattern of measurements of packed-cell fraction ($f_{\mathrm{c,b}}$) in all the present sheep can be adequately represented by a very rapid drop from normal values to a constant:

$$f_{\mathrm{c,b}}=0.26. \qquad (14)$$

Substituting equation 14 in equation 12 gives

$$\lambda_{\mathrm{b/w}}=(29.40\times0.74+43.58\times0.26)+4714\times0.74\times f_{\mathrm{tr}}$$
$$=33.09+3488\times f_{\mathrm{tr}}. \qquad (15)$$

Finally, substituting equation 2 in equation 15 gives $\lambda_{\mathrm{b/w}}$ as a function of time for each sheep in the 1 and 2 ml min^{-1} infusion groups respectively:

$$\lambda_{\mathrm{b/w1}}=37.79+(-0.0148+5.17/M)\times t \qquad (16)$$
$$\lambda_{\mathrm{b/w2}}=40.42+(-0.0148+10.35/M)\times t. \qquad (17)$$

References

1 Weaver BMQ, Staddon GE, Raptopoulos D, Mapleson WW. Partitioning of propofol between blood cells, plasma and deproteinised plasma in sheep. *J Vet Anaesth* 1998; **25**: 19–23

2 Weaver BMQ, Staddon GE, Raptopoulos D, Mapleson WW. Measurement of propofol concentration in sheep blood and plasma: effect of storage at different temperatures. *J Pharmacol Toxicol Methods* 1995; **34**: 199–202

3 Weaver BMQ, Raptopoulos D, Staddon GE, Mapleson WW. Plasma triglyceride concentration during intravenous infusions of propofol and Intralipid in sheep. *J Vet Anaesth* 1996; **23**: 15–9

4 Adam HK, Douglas EJ, Plummer GF, Cosgrove MB. Estimation of ICI 35,868 (Diprivan®) in blood by high-performance liquid chromatography, following coupling with Gibbs' reagent. *J Chromatogr* 1981; **223**: 232–7

5 Pearson MRB. The pharmacokinetics of inhaled anaesthetics in the sheep and ox. Thesis, University of Bristol, 1988: 47, 104, 154, 174, 324–8

6 Webb AI, Weaver BMQ. The density of equine tissue at 37°C. *Res Vet Sci* 1979; **26**: 71–5

7 Weaver BMQ, Staddon GE, Mapleson WW. A puzzle in propofol loss rates from tissue samples in sheep. *Br J Anaesth* 1998; **81**: 630P–1P

8 Mather LE, Selby DG, Runciman WB, McLean CF. Propofol: assay and regional mass balance in the sheep. *Xenobiotica* 1989; **19**: 1337–47

9 Babl J, Doenicke A, Mönch V. New formulation of propofol in an LCT/MCT emulsion: approach to reduce pain on injection. *Eur Hosp Pharm* 1995; **1**: 15–22

10 Lide DR, editor. *Handbook of Chemistry and Physics*, 77th Edn. Boca Raton: CRC Press, 1996; 3–184, 227, 229

11 Tan CH, Onsiong MK. Pain on injection of propofol. *Anaesthesia* 1998; **53**: 468–76

12 Steward A, Allott PR, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *Br J Anaesth* 1973; **45**: 282–93; 1974; **46**: 310(erratum)

13 Büch U, Isenberg JC, Baldauf J, Altmayer P, Büch HP. Interactions between thiopental and volatile anesthetics (halothane and isoflurane) in isolated heart preparations of the rat. *Methods Find Exp Clin Pharmacol* 1992; **14**: 499–505

14 Dale O, Jenssen U. Interaction of isoflurane with the binding of drugs to proteins in serum and liver cell cytosol: an *in vitro* study. *Br J Anaesth* 1986; **58**: 1022–6

15 Dale O, Nilsen OG. Displacement of some basic drugs from human serum proteins by enflurane, halothane and their major metabolites: an *in vitro* study. *Br J Anaesth* 1984; **56**: 535–42

16 Altmayer P, Büch U, Büch HP. Propofol binding to human blood proteins. *Arzneim-Forsch* 1995; **45**: 1053–6

17 Ludbrook GL, Upton RN, Grant C, Martinez A. Prolonged dysequilibrium between blood and brain concentrations of propofol during infusions in sheep. *Acta Anaesthesiol Scand* 1999; **43**: 206–11

18 Shyr M-H, Tsai T-H, Tan PPC, Chen C-F, Chan SHH. Concentration and regional distribution of propofol in brain and spinal cord during propofol anesthesia in the rat. *Neurosci Lett* 1995; **184**: 212–5

19 Upton RN, Ludbrook GL. A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables. *Br J Anaesth* 1997; **79**: 497–504

20 Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, Rowland M. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of ^{14}C-propofol. *Xenobiotica* 1988; **18**: 429–40

21 Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J. Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. *Br J Anaesth* 1990; **64**: 563–70

22 Dogra S, Isaac PA, Cockshott ID, Foy JM. Pulmonary extraction of propofol in post-cardiopulmonary by-pass patients. *J Drug Dev* 1989; **2** (Suppl. 2): 133

23 Knibbe CAJ, Koster VS, Aarts LPHJ, Langemeijer HJM, Danhof M. Pilot study in humans on the pharmacokinetics and safety of propofol 6% SAZN. *Pharm World Sci* 1999; **21**: 239–40

24 Francis B, Green M, Payne C, eds. *The GLIM System—Release 4 Manual*. Oxford: Clarendon Press, 1993

25 Healy MJR. *GLIM: An Introduction*. Oxford: Clarendon Press, 1988

26 Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991

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Antinociceptive properties of neurosteroids III: experiments with alphadolone given intravenously, intraperitoneally, and intragastrically

R. Nadeson and C. S. Goodchild*

Department of Anaesthesia, Monash University, Clayton, Victoria, Australia 3168
**Corresponding author*

The veterinary neurosteroid anaesthetic Saffan® has the same formulation as Althesin® now withdrawn from human use and is a mixture of two neurosteroids, alphadolone, and alphaxalone. The molecular structures of these two pregnanes and their properties as i.v. anaesthetics were reported to be similar. Preliminary experiments showed that alphadolone caused powerful antinociceptive effects without sedation when given i.p. In this study, alphadolone was given to rats (weight 100–200 g) i.v., i.p., and intragastrically. I.v. injections of alphadolone (25 mg kg^{-1}) caused anaesthesia and sedation, whereas i.p. (0.1–100 mg kg^{-1}) and intragastric administration (750 mg kg^{-1}) produced no such effects. Intragastric alphadolone caused antinociceptive effects assessed with the electrical current threshold test (response 2.2×pre-drug control values) without sedation. These effects were reversed at the level of the spinal cord by intrathecally-administered bicuculline (10 pmol). We conclude that a metabolite of alphadolone acetate produced in the liver leads to antinociceptive effects after i.p. and intragastric administration of the parent compound. This antinociception involves spinal cord $GABA_A$ receptors, even though the drug was administered via a non-spinal route.

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After a long search for a new safer i.v. anaesthetic agent, Althesin® was introduced into clinical practice in 1970 and proved to be a highly successful i.v. agent with a very wide therapeutic margin.[1] Much research on the compound followed, and it was used widely for anaesthetic practice all over the world. It is interesting to note, in light of the contents of this report, that all active properties of the mixture of the two steroids called Althesin® were attributed to the alphaxalone content.[1] This assumption has been made repeatedly in the literature based on the statement that alphadolone was present in the mixture merely to improve the solubility of alphaxalone in Cremophor.[2] Thus, no references to the specific physiological properties of alphadolone exist. Althesin® was withdrawn from clinical practice in the late 1980s because of major anaphylactic reactions to Cremophor EL.[3] The mixture is still available for veterinary use (Saffan®).

Experiments reported previously, showed that subanaesthetic doses of Saffan® produce powerful antinociception in rats.[4] This is because of an interaction of one of the components of the mixture with *spinal cord* $GABA_A$ receptors even though the drug was given i.p.[4] Investigations showed that all the sedative and anaesthetic properties of the mixture are a result of the alphaxalone content and all of the antinociceptive properties are a result of the alphadolone content. It is possible that the difference in the activity profile of alphadolone described in those experiments compared with what was reported in the literature during the development of Althesin® may be because of the route of administration. In the early reports on the development of the i.v. anaesthetic combination of alphaxalone and alphadolone the individual agents were probably tested by i.v. administration. By contrast, the experiments reporting antinociceptive effects with no sedation utilized i.p. administration of alphadolone.[4] Thus, in the latter experiments the parent drug would have to pass through the liver and be prone to metabolic transformation before gaining access to the general circulation and the rest of the body. The experiments reported here were performed, first of all to ascertain if i.v. alphadolone did cause anaesthesia as no documentation exists for the effects of this drug given alone. The second aim was to produce a dose response curve for the antinociceptive effect of i.p. alphadolone and to determine if much higher doses than

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those used previously could cause sedation when given i.p. Finally, intragastric administration was investigated as this also delivers the drug first to the liver prior to the drug gaining access to the rest of the body. These experiments might indicate a potential use of the drug as an orally-administered analgesic. The highest dose of alphadolone that could be administered intragastrically was investigated for sedative and antinociceptive effects.

Materials and methods

This work was carried out with permission of the Monash University Standing Committee on Ethics in Animal Experimentation (SCEAE Project No. 93017).

I.v. administration

Four male Wistar rats (weight 100 g) were given 0.25 ml i.v. injections of alphadolone acetate solution (10 mg ml^{-1}; dissolved in 10% Cremophor EL®), into the lateral tail vein using a Hamilton microsyringe and 27-gauge needle. A stopwatch was used to time the following scoring of sedation every 15 s:

0—no righting reflex;
1—righting reflex present but no spontaneous locomotion;
2—spontaneous locomotion observed but uncoordinated;
3—normal locomotion and exploratory behaviour.

These scores were plotted against the time of the observation for each rat.

I.p. administration

Dose response relationship for antinociception

Thirty male Wistar rats (weight 150–200 g) were given a range of doses of alphadolone (0.06, 0.6, 6.0, and 60 mg per kg^{-1} i.p.; n=4, 10, 15 and 4 experiments at each dose, respectively). The drug was suspended in saline solution and injected in a volume of 2 ml kg^{-1}. The rats were observed continuously for signs of sedation such as normal startle reactions to tapping on the Plexiglass restrainer in which they were placed and attempts at exploratory behaviour in the confined space. Antinociceptive thresholds were measured in the tail using noxious electrical current (ECT) as described previously.[5] ECT measurements were made every 5 min until three stable (pre-drug) readings had been obtained. The i.p. injection of alphadolone was then given and the ECT measurements were continued every 5 min for 30 min thereafter. The antinociceptive effect for each dose was calculated as a ratio of control (pre-drug) values as previously described.[5] These values were combined for each alphadolone dose and plotted as means (SEM) to produce a dose response curve.

Intragastric administration

An observer blinded randomized crossover study in five rats

Alphadolone was suspended in 1.0 ml normal saline at a concentration of 375 mg ml^{-1}. This was the highest concentration of drug that could be given to a rat in an intragastric injection. Five male Wistar rats (weight 150–200 g) with lumbar intrathecal catheters implanted as described previously,[6] were randomized to receive on two different occasions on different days either saline or alphadolone given intragastrically in a volume of 2 ml kg^{-1} (750 mg kg^{-1}). This high dose of alphadolone was chosen to assess whether administration of the drug by the gastrointestinal tract could cause sedation and antinociceptive effects. This was a crossover study such that on the following day if a rat had received saline on the first occasion then it received alphadolone on the second occasion and vice versa. This dosing was randomized and the observer making measurements of nociceptive thresholds was blinded to the nature of the treatment. In each experiment, the electrical current thresholds for nociception (ECT) were measured in the neck and the tail every 5 min until three stable readings were obtained. At that stage either saline or alphadolone 750 mg kg^{-1} suspended in saline was instilled into the stomach via an oesophageal needle. Five minutes later and every 5 min thereafter, ECT measurements were performed in the skin of the tail and neck. At 60 min, 10 pmol of bicuculline (a $GABA_A$ receptor antagonist) dissolved in 5 µl 6% dextrose solution was injected intrathecally down a Portex catheter that had been implanted previously in the lumbar subarachnoid space to lie adjacent to the most caudal segments of spinal cord responsible for tail innervation.

ECT measurements were continued for tail and neck electrodes every 5 min for a further 30 min. ECT results for tail and neck electrodes for each treatment (vehicle or alphadolone) at each time point were combined as means (SEM) to produce time response curves.

Results

I.v. administration

All five rats lost the righting reflex and were heavily sedated after i.v. alphadolone acetate 25 mg kg^{-1}. All four rats scored 0 immediately after the i.v. alphadolone. Three rats recovered fully within 90 s and one 270 s after the i.v. injection of alphadolone.

I.p. administration

It can be seen from Fig. 1 that there was a dose-related increase in antinociceptive effect with a maximum response of approximately 2.2× control (pre-drug) values. There were no overt signs of sedation even at the highest dose of i.p. alphadolone 60 mg kg^{-1}. Rats exhibited normal startle reflexes and exploratory behaviour, even after release from the restrainer 30 min after the i.p. injection when the full antinociceptive effects assessed by tail ECT were still present.

Intragastric administration

As shown in Fig. 2 the intragastric vehicle produced no antinociceptive effects in either the tail or neck electrodes. By contrast intragastric alphadolone 750 mg kg^{-1} produced a statistically significant increase in the electrical current thresholds in the skin of the tail and the neck ($P<0.01$; $n=5$; Student's *t*-test). Observation of the animals during this time revealed no differences between the groups with regard to sedation. None of the rats showed overt signs of sedation or a decrease in exploratory behaviour. Intrathecal bicuculline produced no changes in the electrical current threshold in the tail or the neck in those experiments where intragastric vehicle had been administered ($P>0.05$; Student's *t*-test). However, intrathecal bicuculline injection (10 pmol) onto the caudal segments of spinal cord responsible for tail innervation completely reversed the antinociceptive effects of intragastric alphadolone assessed by ECT measurements in the tail. This change was statistically significant when values of ECT readings were compared before and after bicuculline administration (Student's paired *t*-test; $P<0.01$). No change occurred in the neck thresholds after intrathecal bicuculline indicating that the actions of this GABA$_A$ antagonist were confined to caudal segments of the spinal cord.

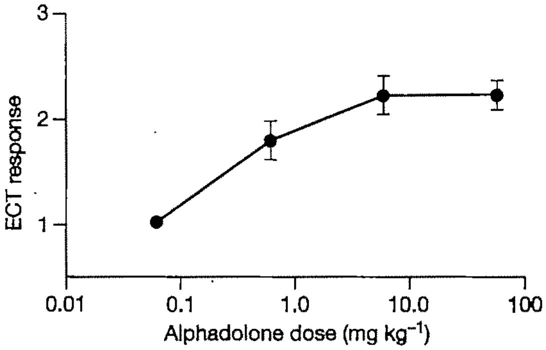

Fig 1 Dose response curve for i.p. alphadolone. Points shown are means and bars±SEM (n=4–15).

Discussion

The present study confirms that alphadolone, given i.v. is an anaesthetic. However, the compound seems to be devoid of anaesthetic and sedative properties when it is given by the i.p. and intragastric routes. It is not uncommon for drugs to have different effects when given by different routes. Before drawing a conclusion about i.p. alphadolone being devoid of sedative properties it is important to determine that enough drug has been given i.p. to achieve an adequate blood level for the effect. The dose of Saffan® that causes anaesthesia in rats is 2 ml kg^{-1} which translates to alphaxalone 18 mg kg^{-1} and alphadolone 6 mg kg^{-1}, a total of 24 mg kg^{-1} neurosteroid. In previous experiments it was shown that alphaxalone 18 mg kg^{-1} given i.p. caused sedation equal to Saffan® 2 ml kg^{-1} and alphadolone 6 mg kg^{-1} caused no sedation.[4] By contrast, alphaxalone given alone caused no antinociceptive effects but alphadolone at 6 mg kg^{-1} produced ECT antinociceptive effects at 2.2× control, a value equal to that caused by Saffan® 2 ml kg^{-1} and also equal to the maximum value of the dose response curve for i.p. alphadolone reported in this paper. It is reported that alphadolone is one-third as potent an alphaxalone in anaesthetic.[2] Thus, from this argument it could be expected a dose of alphadolone three times the total dose alphaxalone that caused anaesthesia (i.e. 3×18=54 mg) would be

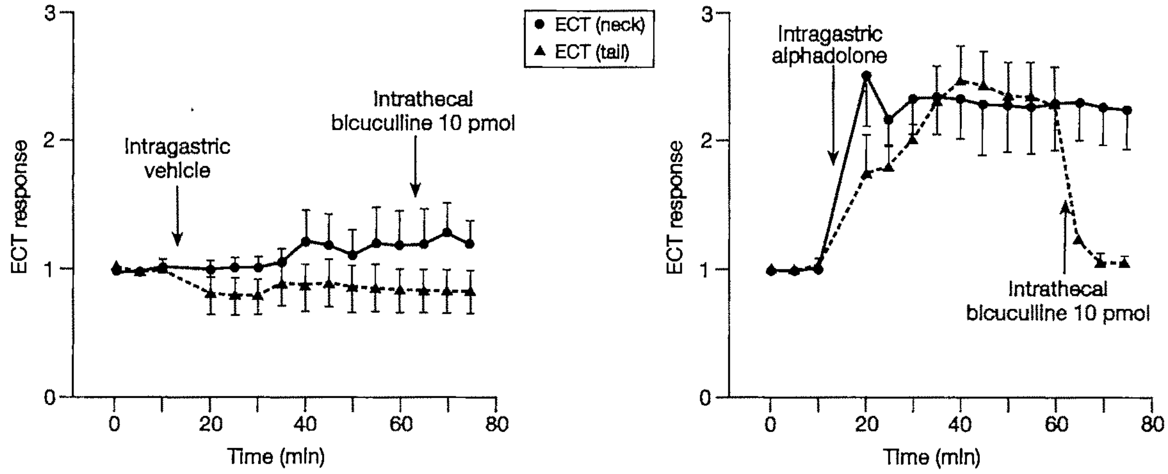

Fig 2 Time response curves showing the ECT antinociceptive effects of intragastric instillation of saline (n=5 rats) and alphadolone 750 mg kg^{-1} (n=5 rats). Alphadolone caused an increase in ECT in the tail and neck. Injection of 10 pmol bicuculline into the lumbosacral intrathecal space reversed the antinociceptive effect in the tail but not the neck.

required for sedation. Doses of alphadolone up to 100 mg kg^{-1} i.p. caused no signs of sedation for a total observation time of 40 min.

Previous experiments have also shown that the antinociceptive effects of Saffan® which were because of the alphadolone content of the anaesthetic mixture were caused by an interaction of the neurosteroid with spinal cord $GABA_A$ receptors as intrathecal injection of the $GABA_A$ receptor antagonist bicuculline reversed the antinociceptive effects.[4] $GABA_A$ antagonists also reversed the spinally-mediated antinociceptive effects of intrathecal injections of water-soluble aminosteroids.[7] Results presented in this paper also show that injection of bicuculline onto the most caudal segments of the spinal cord totally reversed the antinociceptive effects in the tail, the region of the body innervated by the most caudal segments of the spinal cord. As bicuculline is a $GABA_A$ antagonist and as the neck thresholds remained unchanged, it may be conclude that non-sedating doses of intragastric alphadolone produced long-lasting antinociceptive effects mediated by spinal cord $GABA_A$ receptors even though the drug was given intragastrically.

The effect of sex and adrenal steroids on the modulation of neuronal activity, dendritic structure, and behaviour has been well documented.[8–10] These effects result from the regulation of intracellular receptors which direct changes in protein synthesis.[10–12] Therefore, the physiological action of these compounds occurs slowly over hours or days.[12 13] Pioneering work by Seyle 50 yr ago demonstrated that certain pregnanes and androstanes have potent anaesthetic and anticonvulsant effects occurring within a few minutes of administration.[14] Since these early findings, it has become apparent that some steroids can interact directly with a surface membrane receptor–complex to cause a change in central nervous system (CNS) activity.[15 16] Investigators studying the steroid anaesthetic alphaxalone (3α-hydroxy-5α-pregnan-11,20-dione) found that this drug can allosterically positively modulate the γ-aminobutyric acid (GABA) receptor. In subsequent studies alphaxalone and other neuroactive steroids were shown to enhance the inhibitory effect on neuronal excitability of GABA acting at the $GABA_A$ receptor complex.[17–20]

It is now well established that GABA generally and receptors of the $GABA_A$ subclass are involved in spinal cord control of nociception.[21–23] Several different subtypes of $GABA_A$ receptor involved with spinal cord antinociceptive systems have been described.[6] Thus, there is the possibility for these $GABA_A$ receptors to be targeted selectively by analgesic compounds. This effect might be achieved without sedation if they are significantly structurally different from the receptors in the brain that are responsible for the sedative, anxiolytic, anticonvulsant, and anaesthetic effects of a wide variety of compounds.[9 24–28] This idea is supported by the observation of antinociception after recovery from the anaesthetic and sedative effects of propofol, an i.v. anaesthetic drug that causes its sedative and anaesthetic effects by positive modulation of $GABA_A$ receptors.[29] It might, therefore, be expected that two structurally different neurosteroids could interact with different receptors. There is also some suggestion from *in vitro* studies that neurosteroid modulation of native $GABA_A$ receptors obtained from the brain and spinal cord may be different.[30] However, the molecular structures of alphaxalone and alphadolone are very similar and there are no suggestions in published reports of any differences between these two compounds in activity profiles.

Reports in the literature concerned with the development of Althesin® suggest that the alphadolone acetate component of Saffan® is present in the mixture merely to improve the solubility of alphaxalone (the active ingredient) in Cremophor EL.[2] It is also reported that alphadolone is an i.v. anaesthetic like alphaxalone but with one-third the potency.[1] The results of this study, in which alphadolone was given i.v. and all four rats were anaesthetized support those statements. This seems to conflict with the results of the other experiments reported in this paper which show that doses of alphadolone up to 100 mg kg^{-1} given i.p. and 750 mg kg^{-1} intragastrically caused no sedative effects.

It is clear, however, that the drug is absorbed in rats after i.p. and intragastric administration because antinociceptive effects follow such treatment. One possible explanation is that metabolic transformation of the molecule deactivates anaesthetic properties but preserves or imparts antinociceptive properties. In rat brain membranes a well-defined structure-activity relationship has been shown for pregnanes. Studies have shown that the 3α-hydroxyl group on the steroid is required for anaesthetic activity whilst a carbonyl group at position C17 confers greater potency.[31–33] Glucuronide and sulfates have been described to be major metabolites of these neurosteroids.[34] These metabolites may be produced by reaction at the 3α-hydroxyl group in both alphaxalone and alphadolone, and also at the hydroxyl group in the 21 position on the alphadolone molecule after de-acetylation. A drug injected i.p. or given via the gastrointestinal tract is first presented to the liver and neurosteroids are known to have significant first pass metabolism at the liver. As the only difference in the molecular structure between alphadolone and alphaxalone is the hydroxyl group at the 21 position it is suggested that metabolism at this group in the liver is responsible for the differences observed in their biological activity after i.p. and intragastric administration. This metabolite is analgesic and not anaesthetic, a subject worthy of further investigation.

We conclude that the antinociceptive effect of alphadolone after i.p. and gastrointestinal administration may be because of production of a metabolite of the parent compound. This causes spinally-mediated antinociceptive effects by interaction with spinal cord $GABA_A$ receptors. As this effect occurs in the absence of sedation, this suggests a possible clinical use of alphadolone or its metabolite in the management of pain syndromes.

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References

1 Steroid Anaesthesia. Glaxo Symposium on Althesin. *Postgrad Med Bull* 1972; **48** (Suppl 2): 5–139

2 Stock JE. Advances in small animal anaesthesia. *Vet Rec* 1973; **92**: 351–4

3 Watkins J, Allen R, Ward AM. Adverse response to alphadolone/alphaxalone: possible role of IgD. *Lancet* 1978; **2**: 736

4 Nadeson R, Goodchild CS. Antinociceptive properties of neurosteroids II: experiments with Saffan® and its components alphaxalone and alphadolone to reveal separation of anesthetic and antinociceptive effects and the involvement of spinal cord $GABA_A$ receptors. *Pain* 2000; **88**: 31–9

5 Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990; **73**: 273–7

6 Nadeson R, Guo Z, Porter V, Gent JP, Goodchild CS. $GABA_A$ Receptors and spinally-mediated antinociception in rats. *J Pharmacol Exp Ther* 1996; **278**: 620–6

7 Goodchild CS, Guo Z, Nadeson R. Antinociceptive properties of neurosteroids I: spinally mediated antinociceptive effects of water-soluble aminosteroids. *Pain* 2000; **88**: 23–9

8 Twyman RE, Macdonald RL. Neurosteroid regulation of $GABA_A$ receptor single-channel kinetic properties of mouse spinal cord neurons in culture. *J Physiol* 1992; **456**: 215–45

9 Paul SM, Purdy RH. Neuroactive steroids. *FASEB J* 1992; **6**: 2311–22

10 Pfaff DW, McEwen BS. Actions of estrogens and progestins on nerve cells. *Science* 1983; **219**: 808–14

11 Pfaff DW. Features of a hormone-driven defined neural circuit for a mammalian behavior. Principles illustrated, neuroendocrine syllogisms, and multiplicative steroid effects. *Ann NY Acad Sci* 1989; **563**: 131–47

12 Gutierrez M, Martinez V, Cantabrana B, Hidalgo A. Genomic and non-genomic effects of steroidal drugs on smooth muscle contraction *in vitro*. *Life Sci* 1994; **55**: 437–43

13 McEwen BS. Non-genomic and genomic effects of steroids on neural activity. *Trends Pharmacol Sci* 1991; **12**: 141–7

14 Selye H. The anaesthetic effect of steroid hormones. *Proc Soc Exp Biol Med* 1941; **46**: 116–21

15 McEwen BS. What makes a steroid a neurosteroid? Neurosteroids and brain function, sponsored by the Fidia Research Foundation, New Orleans, LA, USA, November 8–9, 1991. *New Biologist* 1992; **4**: 212–6

16 Harrison NL, Vicini S, Barker JL. A steroid anesthetic prolongs inhibitory postsynaptic currents in cultured rat hippocampal neurons. *J Neurosci* 1987; **7**: 604–9

17 Callachan H, Cottrell GA, Hather NY, Lambert JJ, Nooney JM, Peters JA. Modulation of the $GABA_A$ receptor by progesterone metabolites. *Proc R Soc Lond B Biol Sci* 1987; **231**: 359–69

18 Cottrell GA, Lambert JJ, Peters JA. Modulation of GABAA receptor activity by alphaxalone. *Br J Pharmacol* 1987; **90**: 491–500

19 Harrison NL, Majewska MD, Harrington JW, Barker JL. Structure-activity relationships for steroid interaction with the gamma-aminobutyric acidA receptor complex. *J Pharmacol Experiment Ther* 1987; **241**: 346–53

20 Olsen RW, Tobin AJ. Molecular biology of $GABA_A$ receptors. *FASEB J* 1990; **4**: 1469–80

21 Sawynok J. GABAergic mechanisms in antinociception. *Prog Neuropsychopharmacol Biol Psychiatr* 1984; **8**: 581–6

22 Duggan AW, Foong FW. Bicuculline and spinal inhibition produced by dorsal column stimulation in the cat. *Pain* 1985; **22**: 249–59

23 Morris R. Inhibition of nociceptive responses of laminae V-VII dorsal horn neurones by stimulation of mixed and muscle nerves, in the cat. *Brain Res* 1987; **401**: 365–70

24 Purdy RH, Moore PH, Jr, Morrow AL, Paul SM. Neurosteroids and $GABA_A$ receptor function. *Adv Biochem Psychopharmacol* 1992; **47**: 87–92

25 Tanelian DL, Kosek P, Mody I, MacIver MB. The role of the $GABA_A$ receptor/chloride channel complex in anesthesia. *Anesthesiology* 1993; **78**: 757–76

26 Franks NP, Lieb WR. Molecular and cellular mechanisms of anaesthesia. *Nature* 1994; **367**: 607–14

27 Lambert JJ, Belelli D, Hill-Venning C, Callachan H, Peters JA. Neurosteroid modulation of native and recombinant $GABA_A$ receptors. *Cell Mol Neurobiol* 1996; **16**: 155–74

28 Lambert JJ, Belelli D, Hill-Venning C, Peters JA. Neurosteroids and $GABA_A$ receptor function. *Trends Pharmacol Sci* 1995; **16**: 295–303

29 Nadeson R, Goodchild CS. Antinociceptive properties of propofol: involvement of spinal cord gamma-aminobutyric acid A receptors. *J Pharmacol Exp Ther* 1997; **282**: 1181–6

30 Gee KW, Lan NC. Gamma-aminobutyric acidA receptor complexes in rat frontal cortex and spinal cord show differential responses to steroid modulation. *Mol Pharmacol* 1991; **40**: 995–9

31 Turner DM, Ransom RW, Yang JS, Olsen RW. Steroid anesthetics and naturally occurring analogs modulate the gamma-aminobutyric acid receptor complex at a site distinct from barbiturates. *J Pharmacol Exp Ther* 1989; **248**: 960–6

32 Turner JP, Simmonds MA. Modulation of the $GABA_A$ receptor complex by steroids in slices of rat cuneate nucleus. *Br J Pharmacol* 1989; **96**: 409–17

33 Hu Y, Zorumski CF, Covey DF. Neurosteroid analogues: structure-activity studies of benz[e]indenemodulators of GABAA receptor function. 1. The effect of 6-methylsubstitution on the electrophysiological activity of 7-substitutedbenz[e]indene-3-carbonitriles. *J Med Chem* 1993; **36**: 3956–67

34 Holly JM, Trafford DJ, Sear JW, Makin HL. The in vivo metabolism of Althesin (alphaxalone+alphadolone acetate) in man. *J Pharm Pharmacol* 1981; **33**: 427–33

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REVIEW ARTICLE

Hormone replacement therapy (HRT) and anaesthesia

D. Brighouse

Shackleton Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK

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The number of women in Britain using hormone replacement therapy (HRT) is steadily increasing, from an estimated 2% of women aged 40–64 yr in 1987, to 22% in 1994. The projected figure for this age group in the year 2000 is 25%.[51] This increase does not take into account older women who continue to use HRT. Figures from the US suggest a considerably greater use of HRT (42.5% current users, and 20.9% past users in a telephone survey of 1082 randomly selected women).[38] Interestingly, this survey concluded that a large proportion of women felt inadequately informed about the risks and benefits of HRT. As women and their general practitioners become well informed about the potential benefits of HRT, as well as the perceived risks, use may rise more rapidly than projected. The percentage of the population of post-menopausal age is increasing, and the absolute number of HRT-using women presenting for surgery, both elective and emergency, will increase substantially. It is, therefore, relevant for the anaesthetist to be aware of the effects of HRT. Unfortunately, despite the widespread and increasing use of HRT, there are surprisingly few randomized controlled trials (RCTs) investigating its effects; most information derives from numerous observational studies.

What types of HRT are used?

HRT is a generic term, and encompasses the use of unopposed oestrogen therapy, and combinations of oestrogens and progestogens. Unopposed oestrogens are generally used only in women who have had a hysterectomy, because of the associated high rate of endometrial hyperplasia. Cyclical use of progestogens have the disadvantage for patients of producing cyclical withdrawal bleeding, which can be avoided by continuous use of the drug. HRT may be administered orally, transdermally, or as a subcutaneous implant.

The oestrogen and progesterone used for HRT are structurally different chemicals than those used in the oral contraceptive pill, and are of lower potency. The doses of oestrogen (as 17β-oestradiol) in transdermal patches and of conjugated equine oestrogen in oral preparations of HRT are approximately one-sixth as potent as the ethinyl oestradiol used in oral contraceptives. The doses used in HRT are designed to restore oestradiol levels to the lower end of the normal pre-menopausal range.[55] This contrasts with the oral contraceptive pill which is designed to suppress the natural ovulatory cycle.

Studies differ in their conclusions about the relative importance of the different HRT regimens in current use.[11 44] Some studies investigating the effects of HRT do not differentiate between the different preparations available. Further work is needed to address this issue. Finally, there is still relatively little work on the newer drugs such as tibolone, which is a synthetic compound with oestrogenic, progestogenic, and androgenic properties.

Indications for HRT

HRT helps to alleviate the unpleasant symptoms associated with the menopause. RCTs have demonstrated the efficacy of HRT in relieving hot flushes, night sweats, and vaginal dryness. A recent meta-analysis has also confirmed that HRT reduces the depressed mood associated with the menopause.[60]

Considerable interest has been generated by the more long-term potential benefits of HRT therapy, which include a possible reduction in morbidity and mortality from cardiovascular disease (both coronary heart disease and stroke), reduction in morbidity and mortality associated with osteoporosis, and reduction in the cutaneous ageing process. However, there are also potential hazards of HRT therapy. Reported adverse effects include increased risk of malignant disease (specifically breast cancer) and increased risk of venous thromboembolism.

These issues are relevant for the anaesthetist, and an understanding of them will help rationalize the periopera-

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Table 1 Reported effects of HRT on coagulation and fibrinolysis

Measure of coagulation/ fibrinolysis	Effect of HRT
Thrombin production	Dose-dependent increase
Thrombin activity	Dose-dependent increase
Antithrombin III	Decreased
Protein S antigen	Decreased
Factor VII coagulant activity	Increased in oestrogen only preparations
Factor VII antigen	Increased
Plasma fibrinogen	Decreased
Protein C	Increased

tive management of post-menopausal women who present for anaesthesia and surgery.

HRT and venous thromboembolism

Several large studies[11,22,25,29] have consistently demonstrated an increased risk of venous thromboembolism in women using HRT. This risk appears to be restricted to the first year of HRT use, and is estimated at 2–3 times that of non-HRT users. These figures have been confirmed in a recent meta-analysis of relevant studies.[39] It is important to appreciate that although a 2- to 3-fold increase in risk appears high, this only represents one or two additional cases of venous thromboembolism per 10 000 women per year. This increase in risk is still not universally accepted.[13]

Mechanism of increased risk of venous thromboembolism

It is recognized that there are both congenital and acquired risk factors for thromboembolic disease, and that these are both exogenous and endogenous. The Thromboembolic Risk Factors Consensus Group (THRIFT) has published a widely accepted list of both groups of risk factors.[49] HRT affects haematological variables relating to coagulation and fibrinolysis;[36] these are summarized in Table 1.

Inherited thrombophilias

There is a growing body of opinion, which suggests that women who develop venous thromboembolism whilst taking HRT have an underlying thrombophilic tendency that may act additively with a direct effect of oestrogen on the coagulation system.

Inherited thrombophilic defects can be broadly classified as antithrombin deficiencies, or abnormalities of the protein C-protein S system.

The prevalence of inherited thrombophilias varies between 1 in 500 for protein C deficiency, to up to 1 in 14 for Factor V Leiden mutation. Current research suggests that in many cases inherited thrombophilia is not a single but a multi-gene defect. There may well be further, as yet undetectable genetic variants associated with increased risk of venous thromboembolism occurring in relatives of women with proven defects.

Table 2 Factors associated with significantly increased risk of venous thromboembolism compared with control group[33]

Higher activated protein C (APC) resistance
Lower antithrombin activity
High levels of factor IX
High levels of fibrin D-dimer

The prevalence of thrombophilic abnormalities in an asymptomatic population has been estimated at 6.2%, but this rises to 60.2% in patients presenting with venous thromboembolism who have a personal or family history of venous thromboembolism.[57] It has, therefore, been suggested that patients with a personal or family history of venous thromboembolism should be routinely screened for inherited thrombophilic defects.[54] The financial implications of such a policy would be considerable. In an attempt to determine the potential benefits of routine screening, a recent study has investigated the interactions between HRT use and risk of venous thromboembolism in women with and without pro-thrombotic states.[33] The key findings of the study are shown in Table 2.

This study concludes that the combination of HRT use and thrombophilias (especially if multiple) increases the risk of venous thromboembolism 'substantially' (13-fold in the case of women with APC resistance). The authors suggest that it is reasonable to offer coagulation screening to women with a past or family history of venous thromboembolism, and advise that women who are discovered to have an inherited thrombophilia should be counselled about the increased risk before prescription of HRT.

Acquired thrombophilias

Acquired thrombophilias are, by definition, associated with increased risk of thrombosis. The most common cause of acquired thrombophilia is antiphospholipid syndrome, which may occur in isolation, or in association with systemic lupus erythematosus (SLE). There have been small observational studies suggesting that HRT can be safely used in patients with inactive, stable, or moderate disease; a large prospective double-blind placebo-controlled study (Safety of Estrogens in Lupus Erythematosus—National Assessment) is also in progress which should enable definitive evidence-based recommendations to be made.[5] Both antiphospholipid syndrome and oestrogen therapy are quoted risk factors in the THRIFT guidelines, and it would, therefore, seem sensible to use thromboprophylaxis in all women presenting for surgery who have SLE irrespective of whether they are receiving HRT.

Mode of administration of HRT

A recent study suggests that the risk of venous thromboembolism may be related to the mode of administration of

Table 3 National recommendations for pre-operative management of women taking HRT. (CSM=Committee for Safety of Medicines, BNF=British National Formulary, MIMS=Monthly Index of Medical Specialties, THRIFT=Thromboembolic Risk Factors Consensus Group, RCOG=Royal College of Obstetrics and Gynaecology

Recommending body	Comments	Stop HRT pre-op?
CSM	Overall positive balance of risk vs benefit for HRT	Equivocal: 'review need for HRT'
BNF	Restates CSM views	Equivocal: 'may be prudent to review the need for HRT'
MIMS		Yes. Discontinue for 6 weeks before major surgery
THRIFT	Oestrogen therapy is a risk factor for venous thromboembolism in hospitalized patients	No recommendation
RCOG	Routine assessment of thrombotic risk should be made	No indication to stop HRT pre-operatively provided appropriate thromboprophylaxis is employed

HRT. The findings demonstrated increased prothrombin activation peptide and decreased antithrombin activity in women receiving oral oestrogens, but not in those receiving transdermal preparations.[44] This difference between transdermal and oral oestrogen preparations has been confirmed in a recent review,[50] but contradicted in another study[23] which demonstrated significant changes in thrombophilia profile associated with the administration of transdermal oestradiol, and concluded that these changes paralleled those observed with oral HRT.

The exercise habits and fat distribution of women may be as important as HRT use in determining risk of venous thromboembolism. Plasma fibrinogen levels are reduced in physically active women regardless of HRT use.[12] However, a study that controlled for the effects of age, smoking, body mass index and the use of diuretics demonstrated decreased fibrinogen levels and decreased plasma viscosity values in women receiving both unopposed oestrogens and combination therapy.[16]

The possible effect of HRT on arterial thrombosis has not been reported in humans, but in a recent study in monkeys there was no increased risk of occlusive thrombus following a standardized stenosis/injury procedure to the carotid artery.[4] This finding may be relevant when considering the relevance of thrombotic risk following surgery.

Current recommendations for women receiving HRT and undergoing surgery

Unfortunately, there is no evidence base for any of the current recommendations concerning pre- and perioperative management of women using HRT (Table 3). In practice, many women admitted for intermediate or major surgery (especially those presenting for gynaecological surgery) will have additional risk factors that mandate the use of thromboprophylaxis.

The lack of clear guidance reflects the current state of knowledge about pre-operative prediction of post-operative DVT. One recently published RCT suggests significantly increased risk of thromboembolic events following lower extremity fractures and for 90 days after in-patient surgery in women with coronary heart disease taking HRT compared with a control group of non-HRT users.[19] The THRIFT and other studies offer clinical guidelines for identification of patients at risk of venous thromboembolism.[6 28 45] However, at present the clinical utility of pre- and post-operative haemostatic tests that predict post-operative deep vein thrombosis remains unproven.[32]

Issues of relevance to the anaesthetist

If there is an increased rate of idiopathic venous thromboembolism for women in the first year of HRT therapy these women are presumably also at increased risk of perioperative venous thromboembolism during this time. The following questions are relevant.

Is the magnitude of increased risk quantifiable?

There is now consistent data suggesting a 3- to 4-fold increase in relative risk of venous thromboembolism in all women during the first year of taking HRT. The absolute risk of venous thromboembolism for any individual woman will be influenced by other additional risk factors. The only published evidence currently available suggests a substantial (but variable according to particular abnormality) further increase in risk of venous thromboembolism for women with underlying prothrombotic states.[33] There is still no published evidence that enables the anaesthetist to accurately advise a woman taking HRT about the magnitude of the increase in risk of perioperative venous thromboembolism, particularly after the first year of therapy.

Does the risk versus benefit balance favour stopping HRT pre-operatively?

The decision to stop medication pre-operatively implies that the risks of continuing a drug outweigh the risks of stopping it. This debate has been extensively rehearsed in the case of the oral contraceptive pill, where it is clear that the potential risks of stopping the 'Pill' pre-operatively include unwanted pregnancy, the effects of surgery and anaesthesia on that pregnancy, the risks of therapeutic abortion, and the risks of pregnancy itself. The risks of stopping HRT are considerably less dramatic, but equally the risks of continuing it are undefined. This applies particularly to women whose proposed surgical procedure would place them in a high-risk category for venous thromboembolism independent of HRT use. Recent guidelines from the Royal College of Obstetricians and Gynaecologists state that there is no evidence to support a policy of routinely stopping HRT before surgery, and that patients with oestrogen implants should be advised that they must not discontinue their cyclical progestogen.[21]

Should perioperative mechanical and/or pharmaceutical thromboprophylaxis be used?

Clinical guidelines suggest the use of graduated compression stockings for patients at low risk of venous thromboembolism. For patients at moderate or high risk of venous thromboembolism, RCTs strongly recommend the use of prophylactic heparin perioperatively.[33] A recent review of the prevention and treatment of venous thromboembolism consistently recommends the use of low molecular weight heparin prophylaxis for elective hip or knee replacement surgery, and for hip fractures, but does not mention HRT as an additional risk factor.[26]

There is good evidence that administration of either low molecular weight heparin or suitable doses of oral anticoagulants pre-discharge reduces the relative risk of DVT following hip surgery by about 50%.[7] Many women receiving HRT and undergoing surgery will, therefore, receive prophylactic heparin regardless of HRT use.

The decision to use prophylactic heparin in women receiving HRT who would otherwise be in a low risk group cannot at present be made on the basis of RCT evidence, but remains a clinical judgement.

The question of need for ongoing prophylaxis against venous thromboembolism has not been extensively debated in the literature either, despite an awareness of the frequency of late symptomless DVT after total hip replacement. The recent publication of the results of the Pulmonary Embolism Prevention trial, and an accompanying editorial, suggest the need for further research into the role of low dose aspirin for post-hospital discharge thromboprophylaxis.[43 47] It would seem sensible for such research to also consider the use of low dose aspirin for women receiving HRT.

Use of any perioperative pharmacological thromboprophylaxis carries a risk of increased surgical bleeding and subsequent morbidity. Interpretation of published data and clinical decision-making must include consideration of these risks.[10]

HRT and cardiovascular disease

Data from numerous epidemiological studies consistently suggest that the risk of coronary heart disease is reduced by up to 50% by oestrogen replacement therapy. The mechanisms for this have not been fully elucidated. Moreover, the Heart Estrogen Replacement Study (HERS) has confounded the epidemiological data by suggesting that in post-menopausal women with established coronary heart disease there is a trend towards increased risk of cardiovascular disease in the first year of HRT treatment.[27] There has also been controversy about whether the addition of progestogens in combination HRT preparations reduces the benefits of oestrogen therapy, although a large epidemiological study has suggested that combined preparations confer even more benefit than oestrogens alone.[37] A recent review of published RCTs has concluded that whilst HRT improves surrogate measures of risk of atherothrombosis, adverse effects on biological mechanisms related to risk cannot be excluded. [52]

Effects of HRT on lipoproteins

Lipoprotein profile appears to be an important determinant in development of cardiovascular disease. In women, high-density lipoprotein cholesterol (HDL-C) has been shown to have a strong inverse relationship to heart disease risk[2] and observational studies suggest that increasing HDL-C is accompanied by a reduction in heart disease risk. (It is, however, important to note that there have been no specifically directed RCTs to confirm this.) Oestrogen has been consistently demonstrated to increase HDL-C in post-menopausal women, and is therefore considered to be one of the most important mechanisms by which HRT confers cardioprotection. A recent major multi-centre prospective randomized trial concluded that both unopposed oestrogen and various oestrogen–progesterone combination therapies improved lipoprotein profiles and lowered plasma fibrinogen levels.[59]

Several studies demonstrate that HRT reduces low density lipoprotein cholesterol (LDL-C), but the significance of this in relation to cardiovascular risk is unknown. Similarly, effects of HRT on plasma triglyceride levels are inconsistent between studies, and their relevance is not clear.

Effects of HRT on arterial physiology

Progressive arterial endothelial damage occurs with increasing age, and this predisposes to atherosclerosis. Studies on the carotid artery have investigated the effects of HRT. The media layer of the carotid artery wall contains high levels of collagen types I and III. A thick, healthy media is necessary for maintenance of a healthy intimal layer of the vessel wall. In post-menopausal women, the media layer becomes thin (as a result of collagen depletion), allowing the intimal layer to thicken, which predisposes to formation of atheromatous plaques. Use of HRT encourages thickening of the media and delays progress of atheromatous change.[1]

von Willebrand factor, soluble thrombomodulin, and tissue plasminogen activator are all significantly reduced after 6 weeks of HRT. These are markers of endothelial function, and therefore provide further evidence to support the beneficial effects on the cardiovascular system of HRT.[31]

A further study of carotid wall thickness in diabetic and non-diabetic HRT users confirmed the potentially beneficial effect of HRT in both groups.[14]

Another indirect measure of atherosclerosis is systemic arterial compliance—atherosclerotic arteries will be stiffer, and cause a decrease in systemic compliance. HRT (oestrogen or oestrogen–progesterone) has been shown to significantly increase total systemic arterial compliance in both smokers and non-smokers.[35]

The study of carotid and radial artery tonometry in women taking HRT compared with non-treatment control groups has demonstrated a reversal of age-related arterial stiffening in HRT users.[24]

Using another indirect measure of arterial compliance (flow-mediated dilatation in response to reactive hyperaemia), HRT (oestrogen alone or a combined preparation) appears to be protective. Dilatation was decreased compared with pre-menopausal women, but to a significantly lesser extent than in post-menopausal women not using HRT.[34] These findings have been confirmed in a study investigating peripheral vascular flow velocity in post-menopausal women using HRT (oral oestrogen, oestrogen patch, or combined oestrogen–progesterone) compared with a no treatment control group. Peripheral vascular flow velocities were increased in all HRT groups.[30]

These studies support suggestions that HRT has a beneficial effect on blood pressure. Although such an effect has not been consistently demonstrated, this may be a reflection of study design. A recent study has demonstrated significant decreases in both systolic and diastolic ambulatory blood pressures compared with a control group after 1 year of HRT. However, these changes were not revealed by 'office' blood pressure measurement.[53]

Proudler, who examined the effect of combined oestrogen–progestogen HRT on angiotensin-converting-enzyme (ACE) activity, has proposed a further mechanism for the cardioprotective effects of HRT. Serum ACE activity was significantly reduced in treated women compared with untreated controls.[42]

HRT and cardiac function

Several studies have suggested that HRT has a directly beneficial effect on cardiac performance. In one prospective study of combined HRT for 6 months, echocardiographic measurement of left ventricular ejection fraction was significantly increased in the HRT group compared with control, and there was significant improvement in diastolic function.[48] A similar study investigated the effect of HRT on left ventricular diastolic function in both normotensive and hypertensive women before and during treatment, and found significant improvement in several parameters (assessed by echocardiography) of diastolic function in both groups of women after 12 months of HRT.[3]

HRT and cerebrovascular accident

Most studies report a reduction in death rate from stroke in HRT users. However, the data are less consistent than those relating to death from coronary heart disease, and at least one large retrospective study has failed to demonstrate any influence of HRT (either unopposed oestrogens or combination therapy) on the risk of non-fatal haemorrhagic or thromboembolic stroke.[40]

What is the relevance of these findings for the anaesthetist?

Until there is more direct RCT evidence it is unlikely that women will be prescribed HRT for the sole purpose of secondary prevention of coronary heart disease.[56] HRT has effects on cardiovascular physiology that are of uncertain clinical significance. The anaesthetist should be aware of this area of ongoing research; if the potentially cardioprotective effects of HRT are confirmed this would be an important factor in determining the balance of risks and benefits of continuing perioperative use of HRT.

HRT and osteoporosis

Accelerated bone loss in post-menopausal women is well documented, and it is known that this can be prevented by treatment with oestrogens. Untreated osteoporosis is a significant problem; fractured neck of femur accounts for 20% of all orthopaedic bed occupancy in the UK, and 16% of women with fractured neck of femur die as a direct consequence of the fracture.[57] Despite this, controversy continues about the most appropriate treatment, and the duration of benefit of HRT therapy. HRT reduces bone turnover and increases bone mineral density, and it appears that addition of progestogens to oestrogen therapy does not reduce these effects. The protective effect of HRT declines rapidly following cessation of treatment, and the lowest dose of HRT that prevents fracture is unknown. It has been suggested that long-term use of HRT is associated with a 30–50% reduction of hip, spine, and wrist fractures.[8] However, there are other factors associated with development of osteoporosis, and few of the studies of HRT and osteoporosis have been of sufficiently rigorous design to account for the many potentially confounding variables affecting the antifracture efficacy of the drugs being investigated.[46]

A recent epidemiological study of more than 11 000 women found that those using HRT were more likely to have a high level of education, take more physical exercise, and have a higher intake of dietary fibre. The study concludes that caution is required in interpreting observational studies of HRT effects, since selection bias may operate.[41]

Table 4 Relationships between HRT use and risks of malignant disease. (OR=odds ratio, CI=95% confidence interval)

Malignancy	Risks of HRT use
Endometrial cancer[8]	Increased risk with unopposed oestrogen therapy; possible slight increase in risk (not quantified) with combined HRT preparations
Ovarian cancer[17]	Increased risk: OR 1.15 (CI 1.05–1.27)
Breast cancer[9]	Increased risk in current HRT users, proportional to duration of use
Breast cancer[58]	Significant reduction in mortality if HRT has ever been used
Colon cancer[15]	Reduced risk if HRT has ever been used: OR 0.64 (CI 0.46–0.88)
Rectal cancer[15]	Reduced risk if HRT has ever been used: OR 0.46 (CI 0.29–0.72)

HRT and malignant disease

There has been concern that the benefits of HRT may be outweighed by an increased risk of developing malignant disease. The conclusions of recent studies are summarized in Table 4.

Whilst the associations (both positive and negative) between HRT and malignant disease currently have no direct impact on the work of anaesthetists, it is possible that further research in this field may change the pattern of surgical practice for malignant disease in the future.

Conclusions

Numerous questions about HRT remain unanswered. Current research indicates that there are potentially enormous benefits of HRT on morbidity and mortality of postmenopausal women, and its use is likely to increase. As with the oral contraceptive pill, many women may not regard HRT (particularly when used as a topical patch or subcutaneous implant) as medication, and may fail to disclose HRT use unless specifically asked by the anaesthetist.

Although there is clear evidence from RCTs that use of HRT is associated with a small increase in relative risk of venous thromboembolism, there is no such evidence to demonstrate any increased risk of *peri-operative* venous thromboembolism in HRT users. Current advice (based on limited evidence and expert opinion rather than on the results of RCTs) is that HRT use should be regarded as one of the risk factors for venous thromboembolism to be considered when assessing patients pre-operatively. There is no evidence to support stopping HRT pre-operatively. Use of mechanical or pharmacological methods of thromboprophylaxis is recommended for women taking HRT; the choice of thromboprophylaxis will depend upon the number of risk factors for venous thromboembolism.

References

1 Baron YM, Galea R, Brincat M. Carotid artery wall changes in estrogen-treated and -untreated postmenopausal women. *Obstet Gynecol* 1998; **91**: 982–6

2 Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med* 1993; **153**: 2209–16

3 Beljic T, Babic D, Marinkovic J, Prelevic GM. The effect of hormone replacement therapy on diastolic left ventricular function in hypertensive and normotensive postmenopausal women. *Maturitas* 1998; **29**: 229–38

4 Bellinger DA, Williams JK, Adams MR, Honore EK, Bender DE. Oral contraceptives and hormone replacement therapy do not increase the incidence or arterial thrombosis in a non-human primate model. *Arterioscler Thromb* 1998; **18**: 92–9

5 Buyon JP. Hormone replacement therapy in postmenopausal women with systemic lupus erythematosus. *J Am Med Womens Assoc* 1998; **53**: 13–7

6 Clagett GP, Anderson FA Jr, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboembolism. *Chest* 1995; **108**: S312–34

7 Clagett GP, Anderson FA Jr, Geerts W, *et al.* Prevention of venous thromboembolism. *Chest* 1998; **114**: S531–60

8 Clinical Synthesis Panel on HRT. Hormone replacement therapy. *Lancet* 1999; **354**: 152–6

9 Colditz GA, Hankinson SE, Hunter DJ, *et al.* The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; **332**: 1589–93

10 Collins R, Baignent C, Sandercock P, Peto R. Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. *BMJ* 1994; **309**: 1215–7

11 Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; **348**: 977–80

12 DeSouza CA, Stevenson ET, Davy KP, Jones PP, Seals DR. Plasma fibrinogen levels in healthy postmenopausal women: physical activity and hormone replacement status. *J Gerontol Ser A Biol Sci Med Sci* 1997; **52**: M294–8

13 Douketis JD, Ginsberg JS, Holbrook A, Crowther M, Duku EK, Burrows RF. A re-evaluation of the risk for venous thromboembolism with the use of oral contraceptives and hormone replacement therapy. *Arch Intern Med* 1997; **157**: 1522–30

14 Dubuisson JT, Wagenknecht LE, D'Agostino RB Jr, *et al.* Association of hormone replacement therapy and carotid wall thickness in women with and without diabetes. *Diabetes Care* 1998; **21**: 1790–6

15 Fernandez E, La Vecchia C, Braga C, *et al.* Hormone replacement therapy and risk of colon and rectal cancer. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 329–33

16 Frohlich M, Schunkert H, Hense HW, *et al.* Effects of hormone replacement therapies on fibrinogen and plasma viscosity in postmenopausal women. *Br J Haematol* 1998; **100**: 577–81

17 Garg PP, Kerlikowske K, Subak L, Grady D. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; **92**: 472–9

18 Girling J, de Swiet M. Acquired thrombophilia. *Baillieres Clin Obstet Gynaecol* 1997; **11**: 447–62

19 Grady D, Wenger NK, Herrington D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/Progestin Replacement Study. *Ann Intern Med* 2000; **132**: 689–96

20 Greer IA. Epidemiology, risk factors and prophylaxis of venous thrombo-embolism in obstetrics and gynaecology. *Baillieres Clin Obstet Gynaecol* 1997; **11**: 403–30

21 Greer IA, Walker ID. Hormone replacement therapy and venous thromboembolism. *Royal College of Obstetricians and*

Gynaecologists Guidelines 2000; www.rcog.org.uk/guidelines/guideline19.html

22 Gutthann SP, Rodriguez LAG, Castellsague J, Oliart AD. Hormone replacement therapy and the risk of thromboembolism: population based case-control study. *BMJ* 1997; **314**: 796–800

23 Habiba M, Andrea A, Phipps B, al-Azzawi F. Thrombophilia and lipid profile in post-menopausal women using a new transdermal oestrodiol patch. *Eur J Obstet Gynecol Reprod Biol* 1996; **66**: 165–8

24 Hayward CS, Knight DC, Wren BG, Kelly RP. Effect of hormone replacement therapy on non-invasive cardiovascular haemodynamics. *J Hypertens* 1997; **15**: 987–93

25 Hoibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism—a population-based case-control study. *Thromb Haemost* 1999; **82**: 1218–21

26 Hull RD, Pineo GF, Valentine KA. Treatment and prevention of venous thromboembolism. *Semin Thromb Hemost* 1998; **24** (Suppl 1): 21–31

27 Hulley S, Grady D, Bush T, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 1998; **280**: 605–13

28 International Consensus Statement. Prevention of venous thromboembolism. *Int Angiol* 1997; **16**: 3–38

29 Jick H, Derby LE, Wald Meyers M, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; **348**: 981–3

30 Lau TK, Wan D, Yim SF, Sanderson JE, Haines CJ. Prospective, randomized, controlled study of the effect of hormone replacement therapy on peripheral blood flow velocity in postmenopausal women. *Fertil Steril* 1998; **70**: 284–8

31 Lip GY, Blann AD, Jones AF, Beevers DG. Effects of hormone-replacement therapy on hemostatic factors, lipid factors, and endothelial function in women undergoing surgical menopause: implications for prevention of atherosclerosis. *Am Heart J* 1997; **134**: 764–71

32 Lowe GDO. Prediction of postoperative deep-vein thrombosis. *Thromb Haemost* 1997; **78**: 47–52

33 Lowe G, Woodward M, Vessey M, Rumley A, Gough P, Daly E. Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45–64 years. Relationships to hormone replacement therapy. *Thromb Haemost* 2000; **83**: 530–5

34 McCrohon JA, Adams MR, McCredie RJ, *et al.* Hormone replacement therapy is associated with improved arterial physiology in healthy post-menopausal women. *Clin Endocrinol* 1996; **45**: 435–41

35 McGrath BP, Liang YL, Teede H, Shiel LM, Cameron JD, Dart A. Age-related deterioration in arterial structure and function in postmenopausal women: impact of hormone replacement therapy. *Arterioscler Thromb Vasc Biol* 1998; **18**: 1149–56

36 Meade TW. Hormone replacement therapy and haemostatic function. *Thromb Haemost* 1997; **78**: 765–9

37 Nabulsi AA, Folsom AR, White A, *et al.* Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. *New Engl J Med* 1993; **328**: 1069–75

38 Newton KM, Lacroix AZ, Leveille SG, Keenan NL, Anderson LA. The physician's role in women's decision making about hormone replacement therapy. *Obstet Gynecol* 1998; **92**: 580–4

39 Oger E, Scarabin PY. Assessment of the risk for venous thromboembolism among users of hormone replacement therapy. *Drugs Aging* 1999; **14**: 55–61

40 Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997; **350**: 1277–83

41 Persson I, Bergkvist L, Lindgren C, Yuen J. Hormone replacement therapy and major risk factors for reproductive cancers, osteoporosis, and cardiovascular diseases: evidence of confounding by exposure characteristics. *Clin Epidemiol* 1997; **50**: 611–8

42 Proudler AJ, Ahmed AI, Crook D, Fogelman I, Rymer JM, Stevenson JC. Hormone replacement therapy and serum angiotensin-converting-enzyme activity in postmenopausal women. *Lancet* 1995; **346**: 89–90

43 Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep venous thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**: 1295–302

44 Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. *Arterioscler Thromb Vasc Biol* 1997; **17**: 3071–8

45 Scottish Intercollegiate Guidelines Network. *Prophylaxis of Venous Thromboembolism*. Edinburgh: Scottish Intercollegiate Guidelines Network, Royal College of Physicians, 1995

46 Seeman E. Osteoporosis: trials and tribulations. *Am J Med* 1997; **103**: S74–87

47 Sors H, Meyer G. Place of aspirin in prophylaxis of venous thromboembolism. *Lancet* 2000; **355**: 1288–9

48 Taskin O, Gokdeniz R, Muderrisoglu H, *et al.* The effects of hormone replacement therapy on echocardiographic basic cardiac functions in postmenopausal women. *Hum Reprod* 1998; **13**: 2399–2401

49 Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305**: 567–74

50 Tikkanen MJ. The menopause and hormone replacement therapy: lipids, lipoproteins, coagulation and fibrinolytic factors. *Maturitas* 1996; **23**: 209–216

51 Townsend J. Hormone replacement therapy: assessment of present use, costs, and trends. *Br J Gen Pract* 1998; **48**: 955–8

52 van Baal WM, Kooistra T, Stehouwer CD. Cardiovascular disease risk and hormone replacement therapy (HRT): a review based on randomised, controlled studies in postmenopausal women. *Curr Med Chem* 2000; **7**: 499–517

53 van Ittersum FJ, van Baal WM, Kenemans P, *et al.* Ambulatory—not office—blood pressures decline during hormone replacement therapy in healthy postmenopausal women. *Am J Hypertens* 1998; **11**: 1147–52

54 Walker ID. Congenital thrombophilia. *Baillieres Clin Obstet Gynaecol* 1997; **11**: 431–45

55 Waselenko JK, Nace MC, Alving B. Women with thrombophilia: assessing the risks for thrombosis with oral contraceptives or hormone replacement therapy. *Semin Thromb Haemost* 1998; **24** (Suppl 1): 33–9

56 Wells G, Herrington DM. The Heart and Estrogen/ Progestin Replacement Study: what have we learned and what questions remain? *Drugs Aging* 1999; **15**: 419–22

57 Whitehead M, Godfree V. Venous thrombo-embolism and hormone replacement therapy. *Ballieres Clin Obstet Gynaecol* 1997; **11**: 587–99

58 Willis DB, Calle EE, Miracle-McMahill HL, Heath CW Jr. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control* 1996; **7**: 449–57

59 Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; **273**: 199–208

60 Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. *Psychoneuroendocrinology* 1997; **22**: 189–212

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BJA

CASE REPORTS

Abnormal pupillary activity in a brainstem-dead patient

D. Shlugman[1]*, M. Parulekar[2], J. S. Elston[2] and A. Farmery[3]

[1]Neuro Intensive Care Unit, [2] Department of Ophthalmology and [3]Nuffield Department of Anaesthetics,
Radcliffe Infirmary, Oxford OX2 6HE, UK

**Corresponding author*

The pupils in brainstem-dead patients are classically fixed and dilated. We present a case of a brainstem-dead patient whose pupils displayed persistent asynchronous pupillary constriction and dilatation independent of external physical stimuli. Central causes for the phenomenon were excluded leaving an unexplained peripheral cause as the most likely explanation. Early recognition of this phenomenon prevents delay in the diagnosis of brainstem death, lessening to some extent the distress for the family, and facilitating earlier organ donation and allowing the better use of resources.

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We present a unique case of abnormal pupillary movements in a patient who otherwise fulfilled the criteria for brainstem death. The consequences are far reaching. For the relatives, the delay in diagnosis results in undue distress. Organ donation, where applicable, is delayed and may affect the suitability of organs for transplantation. Finally, it is important that brainstem death is recognized early to ensure the most efficient use of limited intensive care unit resources.

Case report

A 35-yr-old woman, with a history of alcohol abuse and depression, for which she had been prescribed amitryptiline, was referred by her general practitioner to the accident and emergency department with a provisional diagnosis of subarachnoid haemorrhage. The previous evening she had drunk one and a half bottles of wine and had complained of a sudden frontal headache. The following morning, she again complained of a sudden headache and collapsed 30 min later.

On admission, she was unresponsive to command with a Glasgow Coma Score of 4/15, and required immediate tracheal intubation and mechanical ventilation of the lungs. The left pupil was fixed and dilated and the right pupil mid-dilated and reacting sluggishly to light. A computed tomography (CT)-scan showed a large left subdural haematoma with significant midline shift (Fig. 1). Mannitol and vitamin K were administered and she was referred to a regional neurosurgical centre.

On arrival at the neurosurgical centre, 3 h after the first presentation, both pupils were fixed and dilated, with absent cough and gag reflexes. In view of these findings, and a significantly deranged clotting profile frequently seen in head injuries (APTT 87 s, INR 3.3), a decision was made not to proceed with surgery.

After excluding potentially reversible causes for coma, the first set of brainstem death tests were performed approximately 6 h after admission. All the brainstem reflexes as laid down in the UK guidelines[1–4] were absent apart from the pupillary responses: the pupils were recorded as reacting to light with a consensual response. It was decided to re-test the patient after a 12 h interval. On re-testing, the pupils were found to be active, but not in response to light. They were continuously observed for a period of 10 min and recorded on video. The pupils were mid-dilated and unequal, with the left pupil being larger. They displayed continuous and independent cyclical constriction and dilatation. The constriction phase lasted 2.5 s, and the dilatation phase 10 s, giving a periodicity of 5 min^{-1}, which was unrelated to ambient light. At the time when one pupil was constricted, the other pupil was almost maximally dilated and vice versa (Fig. 2). No mydriatics had been used at any point. An EEG showed no cerebral activity, even

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during stimulation. Subsequently, two further sets of brainstem tests were performed and the patient was declared brainstem dead more than 24 h after the first set of brainstem death tests. Throughout this period, the pupils remained active, but unresponsive to light. The patient's organs were used for transplantation. Post-mortem examination revealed a 200 ml subdural haematoma over a swollen left cerebral hemisphere with cerebellar tonsillar herniation and necrosis.

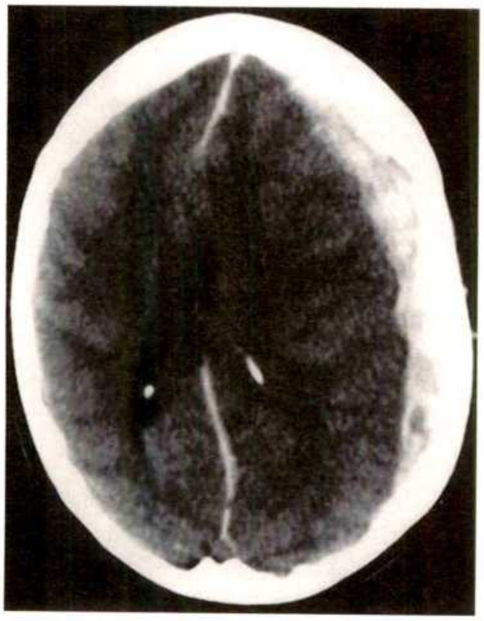


Fig 1 CT-scan showing large left sided subdural haematoma with midline shift.

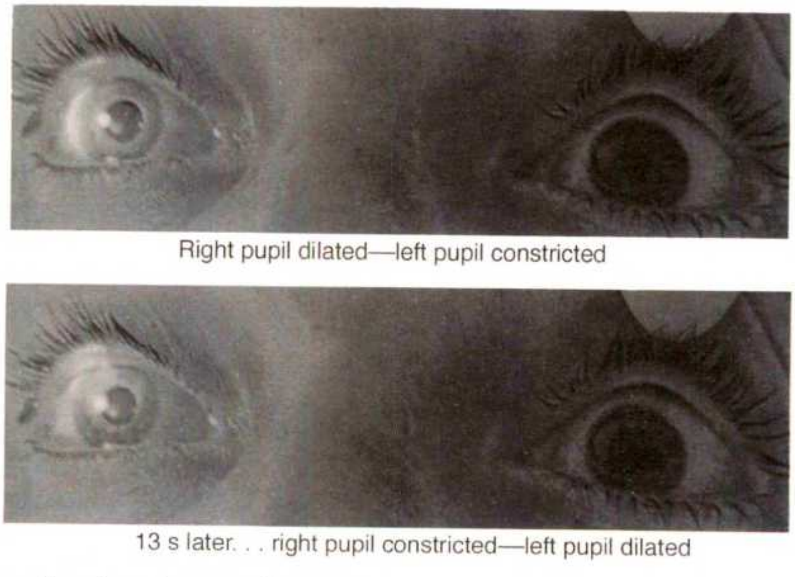
Discussion

In 1976 and 1979, the Conference of Medical Royal Colleges and their Faculties in the UK introduced and developed the concept of brainstem death as being synonymous with the death of the individual, even in the presence of functioning organ systems. Death was defined as 'the irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe'. Strict criteria were laid down for the diagnosis, which could confidently be made at the bedside, without the need for special investigations such as an EEG or cerebral angiography.

To make the diagnosis of brainstem death, a three-stage procedure must be applied. First, certain preconditions must be met showing the patient suffers from a condition that has led to irremediable brain damage. Second, reversible causes of coma such as drug intoxication, hypothermia, metabolic, and endocrine disturbances must be excluded. Third, the absence of brainstem reflexes including the pupillary response to light must be demonstrated.

The bulk of the cranial nerve nuclei lie in close proximity to each other in the brainstem allowing for testing of this structure level-by-level (Fig. 3).[5] The ultimate test of brainstem function is the test for apnoea. If no respiratory effort is seen with a Pa_{CO_2} >6.65 kPa (50 mm Hg), it can be assumed the patient is brainstem dead. It is recommended that the tests are carried out twice, usually a few hours apart. Such tests, by virtue of their simplicity, objectivity, and reproducibility have served to remove ambiguity from a situation fraught with emotion and potential controversy.

This patient had irremediable brain damage, which had been confirmed on CT-scan, and the potential reversible causes for coma had been excluded. Her blood alcohol level on initial presentation the previous day was 80 mg%, the upper legal driving limit in the UK. However, liver



Right pupil dilated—left pupil constricted

13 s later. . . right pupil constricted—left pupil dilated

Fig 2 Spontaneous changes in pupillary size under constant illumination.

dysfunction was evident. The bilirubin levels on previous admissions over the preceding 3 months ranged from 28 to 53 µmol litre^{-1} and the gamma glutamyl transpeptidase, a useful indicator of alcoholic liver disease, was between 289 and 456 iu (normal 7–32 iu). Albumin levels were within the normal range. Before brainstem death tests, the bilirubin was 22 µmol litre^{-1}, blood glucose 5 mmol litre^{-1} and the renal function was normal. An amitryptiline-induced coma was unlikely from the history as it has a half life of 15 h with a range of 9–25 h.

In alcoholics, a coagulopathy is a well-recognized phenomenon.[6] Traumatic head injuries also are often associated with clotting abnormalities. Clotting studies in the context of head injuries are a useful predictor of outcome, with prolongation or shortening of the APTT correlating strongly with death but prothrombin time proving to be of little prognostic value.[7 8] This was borne out by this case where the APTT was 87 s (control 40 s) and INR 3.3 but with a platelet count within normal limits. In this patient's previous admissions, in spite of significant liver dysfunction, her APTT and INR were within the normal range. The coagulopathy was corrected with the administration of fresh frozen plasma.

This patient presented a dilemma. She fulfilled the preconditions and exclusions for brainstem death. There was an absence of cranial nerve and respiratory function but in spite of this, spontaneous pupillary activity was still evident. The pupillary signs raised two important questions. What was the mechanism of the phenomenon, and what were the implications for the diagnosis of brainstem death?

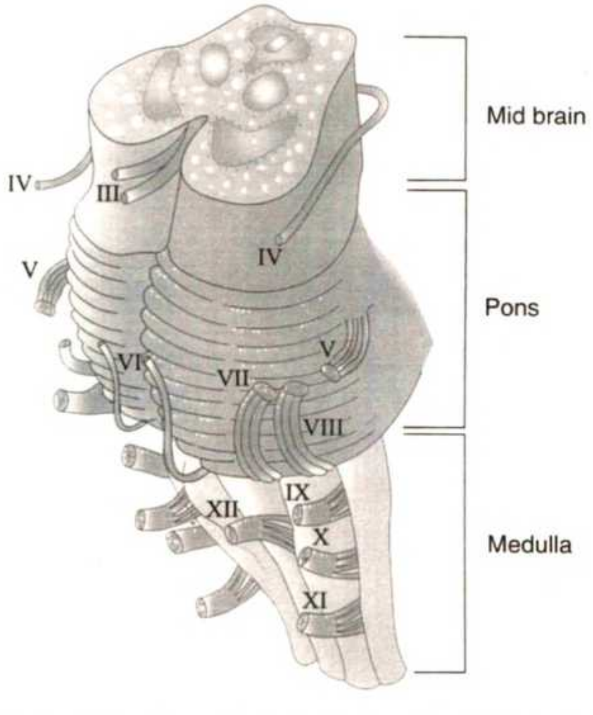


Fig 3 Antero-lateral view of the brainstem showing the close proximity of the cranial nerves (Patten 1996, with permission).

The pupillary response to light requires the presence of an intact reflex arc that passes through the brainstem (Fig. 4). The afferent component is the anterior visual pathway from which fibres pass to synapse in the pretectal nucleus in the mid-brain. The efferent fibres pass to the Edinger-Westphal subnucleii of the oculomotor nerve nucleus, explaining why a bilateral direct and consensual light response is seen when light is shone into one eye. The efferent parasympathetic fibres are a component of the oculomotor nerve, which synapse in the ciliary ganglion in the orbit with the post-ganglionic fibres supplying the pupillary sphincter. A lesion of the efferent pathway results in loss of all ipsilateral pupillary responses, and the pupil is mid-dilated and 'fixed'. Total absence of response to light can occur with total disruption of either afferent or efferent pathways, and with brainstem damage.

There are two reasons why the pupils should be unresponsive to light in this case. First, both oculomotor nerves, the efferent arcs, were shown radiologically and at post-mortem to be compressed against the free edge of the tentorium by the herniating cerebellar tonsils. Second, in brainstem death all the sympathetic and parasympathetic influences are lost and the pupil assumes its position of rest (semi-dilated and fixed). What then was the mechanism of the pupillary activity? This occurred asynchronously and so is unlikely to be a

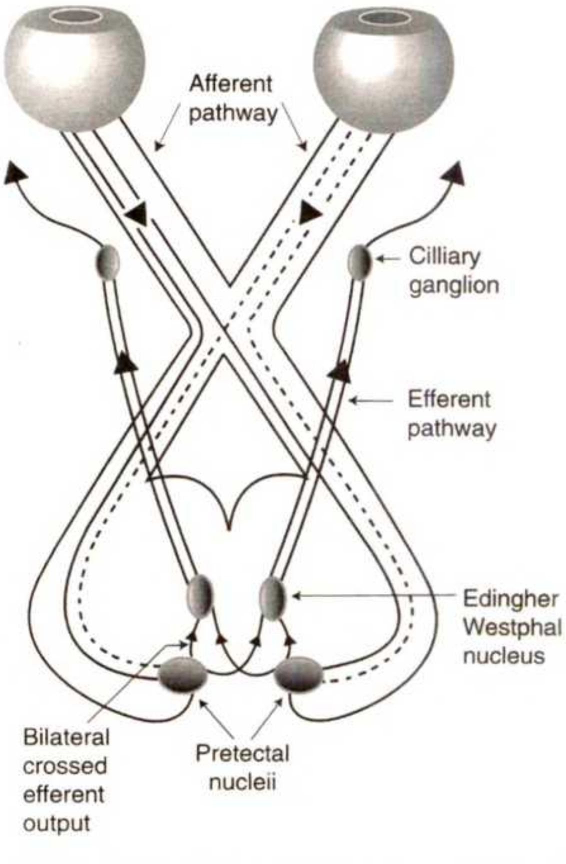


Fig 4 Schematic drawing of the pupillary reflex arc showing crossed bilateral efferent output.

'central' response, which is typically synchronous and bilateral. Light-near dissociation with preservation of the near response only would also produce synchronous pupillary responses. Moreover, for a centrally originating stimulus to produce a pupillary response, requires an intact efferent pathway, which was not the case. As it was asynchronous, it did not represent exaggerated hippus, which is a bilateral, simultaneous fluctuation in pupil size reflecting spontaneous changes in the pupilloconstrictor and pupillodilator balance. Spontaneous pupillary activity has been described as a preterminal event produced by intermittent discharges of dying neurones along the efferent arc, similar to Cheyne-Stokes respiration seen in terminal brainstem damage. However, such activity is typically bilateral and synchronous.[9] The pupillary activity must, therefore, be peripheral in origin, arising either in the ciliary ganglion or the pupillary sphincter. The ciliary ganglion does not have any capacity for spontaneous activity. The iris sphincter, although smooth muscle histologically, is functionally similar to skeletal muscle and does not display spontaneous rhythmicity. Denervated muscle can display supersensitivity to circulating neurotransmitters, but this is likely to be a bilateral synchronous response unlike this case. Moreover, since the phenomenon lasted over 12 h, this is unlikely.

We cannot, therefore, fully explain this phenomenon, nor have we found any similar case report in the literature. This case, in which the spontaneous pupillary activity was initially misinterpreted as a response to light and hence indicative of an intact reflex arc, highlights the importance of thorough technique when testing the pupils. A period of uninterrupted observation is important. This case also shows that pupillary activity in the absence of elicited reactivity does not preclude the diagnosis of brainstem death.

References

1 Working Group of Conferences of Medical Royal Colleges and their Faculties in the United Kingdom. Diagnosis of death. *BMJ* 1976; **2**: 1187–8
2 Working Group of Conferences of Medical Royal Colleges and their Faculties in the United Kingdom. Diagnosis of death. *BMJ* 1979; **1**: 332
3 Criteria for the diagnosis of brain stem death. *J R Coll Physicians Lond* 1995; **29**: 381–2
4 *Code of Practice for the Diagnosis of Brainstem Death.* Department of Health. March 1998
5 Patten J. The brain stem. In: *Neurological Differential Diagnosis.* London: Springer-Verlag 1996; 162
6 Weisberg LA. Alcoholic intracerebral hemorrhage. *Stroke* 1988; **19**: 1565–9
7 Olson JD, Kaufman HH, Moake J, *et al.* The incidence and significance of homeostatic abnormalities in patients with head injuries. *Neurosurgery* 1989; **24**: 825–32
8 Selladurai BM, Vickneswaran M, Duraisamy S, Atan M. Coagulopathy in acute head injury – a study of its role as a prognostic indicator. *Br J Neurosurg* 1997; **11**: 398–404
9 Loewenfeld IE. The light reflex. In: *The Pupil: Anatomy, Physiology and Clinical Applications.* Detroit, MI: Wayne State University Press, 1993; 1: 83–273

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Subdural haematoma after dural puncture headache treated by epidural blood patch

J. M. Davies[1*], A. Murphy[2], M. Smith[2] and G. O'Sullivan[1]

[1]*Department of Anaesthetics, St Thomas' Hospital, Lambeth Palace Rd, London SE1 7EH, UK.*
[2]*Department of Anaesthetics, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK*
**Corresponding author*

Subdural haematoma is a well-documented complication of accidental dural puncture, and is thought to be preventable by prompt treatment with an epidural blood patch. An accidental dural puncture occurred in a 39-yr-old primagravida during the siting of an epidural catheter for pain relief in labour. Twenty hours after the puncture, the mother developed a typical post-dural puncture headache, which increased in severity over the subsequent 24 h. An epidural blood patch was performed at 48 h, and this initially relieved the headache. After discharge from hospital, and 14 days after the dural puncture, the headache recurred, together with

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expressive dysphasia, poor co-ordination and sensory loss in the right arm. A magnetic resonance imaging scan demonstrated a left sided subdural haematoma, which was drained successfully with complete recovery.

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Keywords: analgesic techniques, epidural; complications, post-dural puncture headache; complications, subdural haematoma

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Subdural haematoma is a serious but rare complication of dural puncture. Cases have been reported following accidental dural puncture with an epidural needle, and also after spinal anaesthesia, myelography, discography, and diagnostic lumbar puncture.[1 2] The diagnosis is complicated by the fact that the symptoms are similar to those of a post-dural puncture headache, which in the puerperium has several differential diagnoses, including pregnancy-induced hypertension, meningitis, and cortical vein thrombosis.[3] We describe a case that illustrates the importance of informing general practitioners and patients of the significance of recurrent symptoms after apparently successful treatment of a post-dural puncture headache with a blood patch.

Case report

A previously healthy 39-yr-old Spanish primigravida with well-controlled gestational diabetes had labour induced at 40 weeks of pregnancy. She was 1.60 m tall and weighed 72 kg. She requested epidural analgesia when she could no longer cope with the contraction pains. Before epidural insertion, the anaesthetist explained the procedure and its possible complications, including the risk of dural puncture. The mother was placed in the left lateral position and, under sterile conditions using a loss of resistance to saline technique, a 16-gauge Tuohy needle, with the bevel cephalad, was used to locate the epidural space. The mother was distressed and anxious and found it difficult to remain still, and in the course of the procedure, an accidental dural puncture occurred at the L1/2 interspace. A second attempt at L2/3 was successful and an initial bolus of 15 ml of 0.1% bupivacaine containing fentanyl 2 $\mu g\ ml^{-1}$ was injected slowly through the epidural catheter to induce analgesia. There was no evidence of subarachnoid spread of local anaesthetic and subsequently a 10 ml h^{-1} infusion of 0.1% bupivacaine containing fentanyl 2 $\mu g\ ml^{-1}$ produced a consistent bilateral sensory block to T8, with minimal motor block. The epidural was managed throughout by the anaesthetist (JMD).

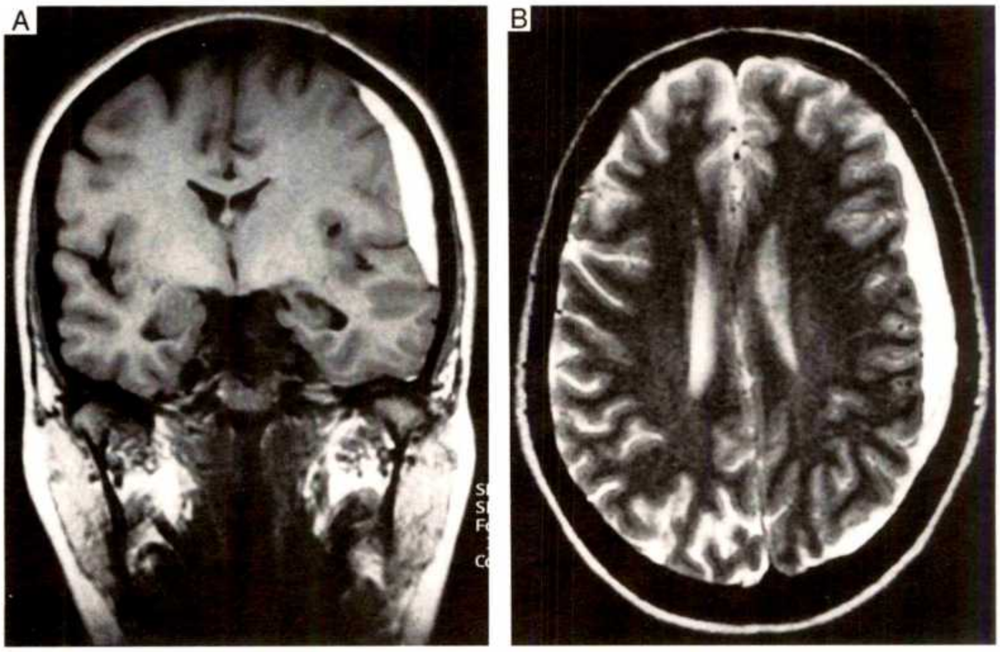

Fig 1 MRI scan, T2 (water white) weighted spin echo; coronal (A) and sagittal (B) views showing left sided subdural haematoma with midline shift.

Seven hours after the epidural had been sited, a top-up was required for perineal pain, by which time 70 ml of the local anaesthetic and opioid mixture had been infused. With the patient sitting upright, 8 ml of 0.75% ropivacaine with fentanyl 100 μg was injected incrementally. When an emergency Caesarean section for fetal distress was carried out 30 min later, the resulting dense bilateral block to T3 provided adequate analgesia. Immediately after delivery, 10 units of i.v. syntocinon was given followed by an infusion of 40 units in 500 ml Hartmann's solution over 4 h. The anaesthetist who had sited the epidural reviewed the patient 2 h after delivery, at which time, on direct questioning, she did not complain of headache.

Twenty hours after the dural puncture and 12 h after the Caesarean section the mother complained to the midwives of a mild fronto-occipital headache. The severity of the headache increased over the subsequent 24 h and, as is typical of a post-dural puncture headache, was relieved by lying flat and deteriorated when the patient mobilized. Oral diclofenac and co-proxamol provided some relief. Thirty-six hours after the onset of the headache, an epidural blood patch was performed at L2/3 under aseptic conditions using 20 ml of autologous blood. The mother remained in bed for 6 h after the procedure and was discharged home 48 h later with total resolution of the headache.

The day after discharge, the patient developed abdominal pain and severe vomiting which persisted for 2 days. Her general practitioner administered an antiemetic after which she gradually improved. One week later, 14 days after her dural puncture, the patient developed a mild frontal headache with expressive dysphasia and was noted to be rather lethargic. Her headache, which was not relieved by either coproxamol or diclofenac, was described as being a 'tight band' around her head. Her general practitioner diagnosed a 'stress headache' and prescribed diazepam. However, within 2 days she was experiencing occasional numbness of her right hand and forearm, poor co-ordination, clumsiness, and the expressive dysphasia had deteriorated. She was seen by a different general practitioner who found no abnormality on neurological examination, but nevertheless, was sufficiently concerned to refer the mother to a neurologist. Before seeing the neurologist, and over the subsequent 2 days, the symptoms worsened, and the general practitioner referred her to the Accident and Emergency Department, where a mild right-handed dysdiadokinesis was noted. On the basis of the worrying history, a magentic resonance imaging (MRI) scan was performed and demonstrated a left hemisphere subdural haematoma, with mild midline shift and compression of the lateral ventricle. Subsequent review of the MRI by a neuroradiologist suggested that the haematoma was up to 3 weeks old (Fig. 1). The patient was transferred to a neurosurgical unit where a craniotomy was performed and the clot was evacuated. She was discharged home 5 days later after an uneventful recovery and with full resolution of her symptoms. A follow-up MRI scan and MR angiogram were normal and the mother remains fit and well.

Discussion

Chronic subdural haematoma is a rare but well-documented complication of dural puncture.[1] It often presents with symptoms similar to those of post-dural puncture headache, for example headache, nausea, and photophobia but without neurological features.

In 1898, Bier subjected himself to spinal anaesthesia and suffered a severe headache, which resolved over the ensuing 9 days. He proposed that the escape of a considerable amount of cerebrospinal fluid (CSF) could bring about such effects.[4] Based on this idea, in 1943, Kunkle and colleagues suggested that the leak of CSF through a dural puncture caused a decrease in CSF pressure within the subarachnoid space, allowing the brain and the meninges to sag. The resulting traction on pain-sensitive vascular structures, which anchor the brain to the cranium, causes headache, particularly in the upright position.[5] It is thought that the traction on the bridging veins combined with compensatory vasodilatation of these vessels as a result of the low CSF pressure, can occasionally result in tearing of the veins and, hence, unilateral or bilateral subdural haematoma.[1] Other causes of subdural haematoma in young people, such as arteriovenous malformations, head injury, and rupture of cerebral aneurysms should be excluded using angiography.

The most effective treatment of severe or persistent post-dural puncture headache is an epidural blood patch, first introduced in 1960 by Gormley.[6] Because the postulated pathogenesis of subdural haematoma in these circumstances is reduced CSF pressure, it has been suggested that failure to treat post-dural puncture headache with a prompt epidural blood patch may be a factor in haematoma formation.[1 2] Our case report and another recent publication[7] suggest that one cannot rely on an epidural blood patch to prevent the development of a subdural haematoma when the patch is performed after the onset of the symptoms of a CSF leak. It was the opinion of the radiologist that the haematoma had developed at or near the time of the original puncture suggesting perhaps that a prophylactic blood patch might be a more appropriate method of prophylaxis against the complications of dural puncture. The efficacy and benefit of prophylactic *versus* therapeutic blood patch in obstetric patients is speculative and a prospective, randomized comparative study would be needed to address this question.

In our obstetric unit, all dural punctures are audited and there is a procedure for the management of accidental dural puncture and post-dural puncture headache. If a dural puncture is known to have occurred during epidural insertion, the anaesthetist throughout labour manages the epidural but the type of delivery is not dictated. A consultant obstetric anaesthetist is informed and the mother is followed up on the postnatal ward. In the event of persistent post-dural puncture headache an epidural blood patch is performed within 24 h of the onset of the headache. The mother is reviewed daily until discharge and is advised, that if she experiences any further headaches or unexplained symptoms, to return to the Obstetric Day Assessment Unit or the Labour Ward where she will be seen by a consultant anaesthetist. A copy of the patient's discharge summary is sent to the general practitioner and community midwife, who visits daily for 10 days. Subsequent to this patient, the consultant anaesthetist now writes a discharge letter to the general practitioner providing information about the dural puncture and its management, and advising that the mother be referred back to the Obstetric Day Assessment Unit in the event of further complications. A recent study, which highlighted the poor understanding of post-dural puncture headache amongst general practitioners, prompted the authors' to design pamphlets for general practitioners and patients with the intention of improving the early recognition and management of post-dural puncture headache.[8]

Failure to recognize these rare cases of subdural haematoma can have permanent and fatal consequences.[9 10] Therefore, in the puerperium, it is crucial to investigate persistent or recurrent headache, particularly those associated with neurological signs, and a CT or MRI scan should be performed as appropriate.

Whilst an epidural blood patch usually provides almost instantaneous relief for a post-dural puncture headache, its longer-term efficacy is probably only 60–70%.[11 12] This case suggests that an epidural blood patch, contrary to popular belief, may not provide protection against the more devastating complications of a dural puncture and in addition highlights the ongoing responsibility anaesthetists have to mothers who suffer an accidental dural puncture.

References

1 Vos PE, de Boer WA, Wurzer JA, van Gijn J. Subdural hematoma after lumbar puncture: two case reports and review of the literature. *Clin Neurol Neurosurg* 1991; **93**: 127–32

2 Reynolds F. Dural puncture and headache: avoid the first but treat the second. *BMJ* 1993; **306**: 874–6

3 Stocks GM, Wooller DJA, Young JM, Fernando R. Postpartum headache after epidural blood patch: investigation and diagnosis. *Br J Anaesth* 2000; **84**: 407–10

4 Brownridge P. The management of headache following accidental dural puncture in obstetric patients. *Anaesth Intens Care* 1983; **11**: 4–15

5 Kunkle EC, Ray BS, Wolff HG. Experimental studies on headache: analysis of the headache associated with changes in intracranial pressure. *Arch Neurol* 1949; **49**: 323

6 Gormley JB. Treatment of post-spinal headache. *Anesthesiology* 1960; **21**: 565–6

7 Diemunsch P, Balabaud VP, Petiac C, *et al.* Hematome sous dural bilateral après analgésie péridurale. *Can J Anaesth* 1998; **45**: 328–31

8 Schneider GT, Price CM, Thornberry EA. Postdural puncture headache (PDPH): easily accessible information for the general practitioner. *Int J Obstet Anesth* 1997; **6**: 208

9 Edelman JD, Wingard DW. Subdural hematomas after lumbar dural puncture. *Anesthesiology* 1980; **52**: 166–7

10 Newrick P, Read D. Subdural haematoma as a complication of spinal anaesthesia. *BMJ* 1982; **285**: 341–2

11 Williams EJ, Beaulieu P, Fawcett WJ, Jenkins JG. Efficacy of epidural blood patch in the obstetric population. *Int J Obstet Anesth* 1999; **8**: 105–9

12 Taivainen T, Pitkanen M, Tuominen M, Rosenberg PH. Efficacy of epidural blood patch for postdural puncture headache. *Acta Anaesthesiol Scand* 1993; **37**: 702–5

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Incremental spinal anaesthesia for elective Caesarean section in a patient with Eisenmenger's syndrome

P. J. Cole*, M. H. Cross and M. Dresner

Department of Anaesthesia, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

**Corresponding author*

We describe a new approach to anaesthesia for elective Caesarean section in a woman with Eisenmenger's syndrome. Incremental regional anaesthesia was performed using a microspinal catheter and haemodynamic monitoring included transthoracic bioimpedance cardiography. This approach allowed the disadvantages of general anaesthesia and invasive cardiac output monitoring to be avoided.

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Eisenmenger's syndrome includes any condition in which a communication between the systemic and pulmonary circulations gives rise to pulmonary vascular disease, which in turn causes a right to left shunt. It is a rare condition that poses a significant risk of maternal death, with the mortality of between 30 and 70%, having changed little over the last 50 yr.[1–4] Eighty per cent of deaths occur between the 2nd and 30th post-natal day,[1] but it remains unclear whether the choice of anaesthetic technique influences the outcome. The primary anaesthetic goal is to avoid any haemodynamic change that might increase the right to left shunt and thereby increase hypoxaemia. With this in mind, many practitioners have avoided regional anaesthetic techniques in favour of general anaesthesia. We describe a regional technique that, to our knowledge, has not been previously reported in this context.

Case report

A 28-yr-old woman with complex cyanotic heart disease was referred at 27 weeks gestation to our Antenatal Anaesthetic Clinic. Her cardiac pathology had been classified as a form of Eisenmenger's syndrome and consisted of mitral atresia, a single ventricle, atrial septal defect, transposition of great arteries with pulmonary hypertension, and subsequent pulmonary vascular obstructive disease. Her condition had not been considered amenable to surgery, other than by heart/lung transplant. This was contraindicated by her marked thoracic scoliolis, which had resulted in significant restrictive respiratory disease. Her medical management consisted of nifedipine and frusemide, and she underwent regular venesection for secondary polycythaemia to maintain haemoglobin at approximately 15 g dl^{-1}. Despite counselling and advice that pregnancy carried a significant risk of death, she was determined to have children. After four miscarriages, her fifth pregnancy had progressed without significant problems apart from some fetal growth retardation.

Her condition at 27 weeks gestation had deteriorated from her non-pregnant state, with central cyanosis and dyspnoea, worsening with speech. At that time, the obstetricians had made a provisional plan to perform an elective Caesarean section (LSCS) at 35 weeks, so the anaesthetic choices and risks were explained to the patient and her family at an Anaesthetic Antenatal Clinic consultation. A formal management plan was reserved until nearer the delivery date in order to take changes in her condition into consideration. She was subsequently admitted at 29 weeks because of increasing dyspnoea, and her diuretic and thromboprophylactic treatments were optimized. Because of continuing dyspnoea and poor fetal growth, it was decided to perform the LSCS at 32 weeks.

In the anaesthetic room, the patient was dyspnoeic with an oxygen saturation of 77% in air and an arterial pressure of 120/60. Peripheral venous and radial arterial lines were sited followed by a right internal jugular triple lumen catheter that revealed a central venous pressure (CVP) of 13 mm Hg. Meticulous attention was paid to the avoidance of bubbles in lines and syringes because of the risk of paradoxical embolus.

With the patient in the sitting position, a 32-gauge Ruschke catheter was inserted through a 24-gauge Sprotte spinal needle at the third to fourth lumbar spinal interspace. In order to avoid maldistribution of the injected solution, the catheter was pushed only 2–3 cm past the needle tip. Before giving any drugs through the catheter, the patient was placed in the supine position with left lateral tilt, and oxygen therapy was instituted via a Hudson mask. This increased the oxygen saturation from 77 to 80%. Non-invasive cardiac output monitoring was then established using the transthoracic bioimpedence method (NCCOM3, BoMED Manufacturing, Irvine, CA, USA), indicating a cardiac output of 3.0 litre min^{-1}. Antibiotic prophylaxis was administered. No formal fluid preload was performed, but a slow infusion of 0.9% saline was commenced.

After first giving diamorphine 300 µg through the spinal catheter, incremental doses of 0.25 ml 0.5% hyperbaric bupivacaine were titrated against anaesthetic and haemodynamic effects. Over a period of 30 min, a total of 2.25 ml produced a block height to the eighth thoracic dermatome tested to touch with blunt forceps. During this time oxygenation remained unchanged, arterial pressure fell by 10 mm Hg, cardiac output rose to 3.7 litre min^{-1}, and CVP gradually fell to 6 mm Hg. This latter change was corrected with a 300 ml bolus of saline. No maternal symptoms or fetal distress occurred.

The LSCS proceeded uneventfully without pain or discomfort and no further drugs were administered through the spinal catheter. The usual bolus of oxytocin was omitted in favour of uterine massage and a slow oxytocin infusion. This produced adequate uterine contraction and blood loss was minimal. During uterine repair, an episode of dizziness coincided with a decrease in arterial pressure to 93/50. A bolus of ephedrine 3 mg restored the arterial pressure, increased the cardiac output to its highest level of 4.9 litre min^{-1}, and resolved the dizziness. This was the largest haemodynamic change during the whole procedure. A total of 1500 saline was given. Haemodynamics and oxygenation in air were almost identical to pre-operative values at the completion of surgery.

Post-operative analgesia consisted of rectal diclofenac 100 mg at the end of surgery, followed by regular 8 hourly doses of 50 mg supplemented by a codeine/paracetamol combination on request. The patient was transferred to the Obstetric High Dependency Unit from where, after 36 h, she was transferred to a routine post-natal ward. At 48-h follow-up, she gave maximal scores for peri-operative comfort and overall satisfaction, experiencing no nausea, vomiting, or spinal headache. After 10 days she was discharged from hospital, and 1 yr later both the patient and child are doing well. Ignoring medical advice, she is now planning another pregnancy.

Discussion

The exact mortality for Eisenmenger's syndrome in pregnancy is unknown, as cases that are unsuccessful are often not reported in the literature. Two recent reviews found the mortality was found to be 36 and 40%[1 3] whilst another quoted a figure of 70%.[4] Pregnancy prevention or early termination of pregnancy is the preferred measure for improving long term survival in women of childbearing age. Despite this, 80% of women with Eisenmenger's syndrome, who are pregnant, have been given the diagnosis before the pregnancy.[1]

Whatever anaesthetic technique is chosen the principle remains the same. The cardiac output must be maintained and the systemic vascular resistance (SVR) must not be allowed to fall. This should ensure that there is minimal change in the amount of right to left shunt.

Several factors affected our anaesthetic plan. First, the patient wanted to be awake at the time of delivery with her partner present. Second, whilst traditional teaching has been that general anaesthesia is to be preferred to a regional technique we felt that general anaesthesia posed clear risks and disadvantages. These included the potential for increasing pulmonary vascular resistance in response to catecholamine release after laryngoscopy, during anaesthesia and in recovery given the relatively poor pain control achievable with systemic opioids. Intermittent positive pressure ventilation increases intrathoracic pressure, reduces venous return and increases pulmonary arterial pressure. This would in turn increase the right to left shunt in this patient. Also, general anaesthesia has the potential to exacerbate her respiratory disease, thereby increasing post-operative hypoxia. These hazards are avoided by regional anaesthesia, although the level of block required using a regional technique might produce excessive sympathetic block and an uncontrolled decrease in the SVR.[2] Epidural anaesthesia has been used successfully in this condition[5–7] and, because of its slow onset, this technique reduces the chances of precipitous haemodynamic changes. However, epidural anaesthesia can produce patchy or incomplete sensory block, which may result in undesirable sympathetic stimulation, or the need to convert to general anaesthesia. In addition, the large amount of local anaesthetic that is required when an epidural is used may result in blood concentrations high enough to cause myocardial depression in such a vulnerable patient. Spinal anaesthesia is, we believe, more reliable, but a single shot approach is too haemodynamically unstable.

Our experience with incremental spinal anaesthesia using spinal catheters[8] gave us confidence that haemodynamic stability could be maintained, particularly given that aortocaval compression would be less of a problem at 32 weeks with a growth retarded fetus.

We proceeded with the LSCS with a block height to the 8th thoracic dermatome (T8) tested to touch with blunt forceps. A study investigating the block height required for Caesarean section, concluded that absent touch sensation to the level of T4 was necessary when using a solution of plain local anaesthetic.[9] This study needs to be repeated with spinals using lipid soluble opioids as our audit results have shown T6 to be adequate in the presence of diamorphine 300 μg. We would not normally recommend proceeding with a block as low as T8, but in this case we were anxious to minimize the sympathetic block and were confident the level could be rapidly increased if pain ensued.

Our choice of monitoring requires some comment. Pulse oximetry was the most practical way of continuously assessing the degree of right to left shunt during the perioperative period. Invasive arterial pressure monitoring was considered mandatory simply because of the immediacy of the information provided. The assessment of cardiac filling and output was not so straightforward given the unusual anatomy of the heart. CVP may not have correlated well with left ventricular end diastolic pressure, but central access was certainly required in case of the need for resuscitation. In fact, initial readings and waveforms were entirely appropriate for the patient's clinical condition, and subsequent changes in CVP followed the clinical picture.

Cardiac output monitoring was not considered of critical importance, given that we expected the heart to be of relatively fixed, low output. However, the BoMED, with which we have extensive experience, is a simple non-invasive method for cardiac output monitoring that is quicker, less technically demanding,[10] and more comfortable than Doppler echocardiography. Once again, this monitor gave information and trends that fitted the clinical picture. The anatomical anomolies in this patient (mitral atresia and transposition of the great arteries) would have rendered the pressures measured with a pulmonary artery flotation catheterization (PAFC) of doubtful or potentially misleading values. Thus, the decision to avoid the potential hazards of a PAFC was justified.

We chose not to give oxytocin as a bolus because it causes direct vasodilatation and reduces SVR with a compensatory increase in heart rate and cardiac output in first trimester pregnant women.[11 12] We have confirmed these findings in healthy term pregnant women under spinal anaesthesia in our own as yet unpublished work. Significant hypotension after 10 units oxytocin was prevented by a mean increase in cardiac output of 80% measured with the BoMED. It was our assumption that our patient would be unable to mount such a response. Indeed, in the survey by Weiss and colleagues[1] two of the patients who had a complicated course after systemic hypotension did so after oxytocin was administered. The policy of using uterine massage followed by a slow oxytocin infusion proved safe and effective in this case.

Whether regional or general anaesthesia is used. the importance of maintaining SVR has already been emphasized. The prophylactic and therapeutic use of vasoconstrictor drugs, therefore, seems logical and attractive. Ephedrine is the most commonly used vasoconstrictor in obstetric practice, but the tachycardia it can produce would be undesirable in a patient with Eisenmenger's syndrome. Whilst a norepinephrine infusion has been documented to maintain SVR throughout the peri-operative period,[13] an excessive dose of metaraminol has caused near catastrophe,[14] presumably by increasing pulmonary vascular resistance and increasing the degree of right to left shunt. Directly acting vasoconstrictors also have the potential to compromise placental perfusion. These agents, therefore, need to be used with caution. It was decided to proceed initially with our familiar agent, ephedrine, and change to a direct acting vasoconstrictor if necessary. In the end, by using an incremental spinal approach to anaesthesia, only 3 mg of ephedrine was required during the procedure and post-operative period.

Although there is general agreement that patients with significant cardiac disease should have their obstetric care at a centre where expert cardiological and cardiac surgical help is available, debate exists about whether elective LSCS should occur on the labour ward or in the cardiac operating theatre. Successful conversion of a planned cardiac operation during the third trimester to a combined emergency LSCS and cardiac operation is well documented. With the advent of improved neonatal care, physicians managing these patients are tending to move to an elective combined approach if patients decompensate during the third trimester with a surgically correctable lesion.

However, it is particularly uncommon for patients with significant cardiac disease, undergoing an elective LSCS (without concomitant cardiac surgery), to require emergency cardiac surgery. For this reason it is probably safe for the operation to be conducted on the labour ward.[15] The theatre staff on the labour ward may be unfamiliar with some of the monitoring required and with some of the drugs used and for this reason we may opt to carry out the LSCS in a cardiac operating theatre. This is despite the knowledge that cardiac surgery will not be an option and that the obstetric and neonatal staff are working in a strange environment. The risks and benefits of each operating theatre are always considered before making a final decision about the place of delivery.

The FDA withdrew approval to use small-bore catheters for continuous spinal anaesthesia in April of 1992 after several case reports of cauda equina syndrome.[16] The view in the UK was that this problem was because of the pooling of excessive doses of hyperbaric 5% lidocaine rather than the catheters *per se*. Although microspinal catheters were never withdrawn in the UK, the dwindling world market led to manufacturers abandoning their production. The Ruschke kit used for this case report is, therefore, no longer available. Larger catheters may introduce an unacceptable incidence of post-dural puncture headache, as they have to be passed through an even larger spinal needle. An alternative is the Braun 'catheter-over-needle' system[17] where a 22-gauge spinal catheter covers a 27-gauge Quinke spinal needle with the sharp point outside the catheter.

References

1 Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *J Am Coll Cardiol* 1998; **31**: 1650–7

2 Foster JM, Jones RM. The anaesthetic management of the Eisenmenger syndrome. *Ann R Coll Surg Engl* 1984; **66**: 353–5

3 Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. *Br J Obstet Gynaecol* 1998; **105**: 921–2

4 Ramin SM, Maberry MC, Gilstrap LC, 3rd. Congenital heart disease. *Clin Obstet Gynecol* 1989; **32**: 41–7

5 Spinnato JA, Kraynack BJ, Cooper MW. Eisenmenger's syndrome in pregnancy: epidural anaesthesia for elective Cesarean. *N Engl J Med* 1981; **304**: 1215–7

6 Rosenberg B, Simon K, Peretz BA, Roguin N, Birkhahn HJ. Eisenmenger's syndrome in pregnancy: controlled segmental epidural block for Cesarean section. *Reg Anaesth* 1984; **7**: 131–3

7 Tibaldi G, Marchi L, Huscher M, Forlini G. Anaesthesia for Cesarean section in a pregnant woman with Eisenmenger's syndrome: description of a clinical case. *Minerva Ginecol* 1988; **40**: 145–6

8 Dresner M, Maclean A. Anaesthesia for Caesarean section in a patient with Klippel-Feil syndrome. The use of a microspinal catheter. *Anaesthesia* 1995; **50**: 807–9

9 Russell IF. Levels of anaesthesia and intraoperative pain at Caesarean section under regional block. *Int J Obstet Anesth* 1996; **5**: 236–9

10 Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedence. *Br Heart J* 1990; **63**: 93–7

11 Weis FR, jnr, Markello R, Mo B, Bochiechio P. Cardiovascular effects of oxytocin. *Obstet Gynecol* 1975; **46**: 211–4

12 Secher N, Arnsbo P, Wallin L. Haemodynamic effects of oxytocin and methyl ergometrine on the systemic and pulmonary circulations of pregnant anaesthetized women. *Acta Obstet Gynecol Scand* 1978; **57**: 97–103

13 Sammut MS, Paes ML. Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome. *Br J Anaesth* 1997; **79**: 810–2

14 Bird TM, Strunin L. Anaesthesia for a patient with Down's syndrome and Eisenmenger's complex. *Anaesthesia* 1984; **39**: 48–50

15 Parry AJ, Westerby S. Cardiopulmonary bypass during pregnancy. *Ann Thor Surg* 1996; **61**: 1865–9

16 Rigler M, Drasner K, Krejcie TC, *et al.* Cauda equina syndrome after continuous spinal anaesthesia. *Anesth Analg* 1991; **92**: 275–81

17 Mollmann M, Van Steenberge A, Sell A, *et al.* Spinocath, a new approach to continous spinal anaesthesia—preliminary results of a multicenter trial. *Int Monitor* 1996; **8**: 74

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Undiagnosed myasthenia gravis unmasked by neuromuscular blockade

M. F. Dunsire*, S. G. Clarke and J. J. Stedmon

Department of Anaesthesia, Fremantle Hospital, Alma Street, Fremantle WA 6160, Australia
**Corresponding author: Present address: Department of Anaesthesia, Medway Hospital, Windmill Road, Gillingham, Kent ME7 5NY, UK*

Myasthenia gravis is an uncommon autoimmune disease resulting in destruction of the post-synaptic nicotinic receptors at the neuromuscular junction. We describe a 43-yr-old, 95 kg patient who presented for elective laparoscopic cholecystectomy. She was given vecuronium 10 mg to facilitate tracheal intubation. At the end of the procedure the patient could not maintain adequate spontaneous ventilation despite administration of two doses of neostigmine 2.5 mg. Subsequent investigation led to a diagnosis of myasthenia gravis. We discuss the investigation, diagnosis, and subsequent management of such a patient and emphasize that tactile estimation of the train-of-four ratio is not a reliable indicator of adequate recovery of neuromuscular function.

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Myasthenia gravis is a well recognized cause of muscle weakness and can prolong the action of non-depolarizing neuromuscular blocking agents.[1 2] The dose of these drugs is, therefore, reduced in such patients or they are not used. We describe a case in which vecuronium 10 mg was given to a patient with undiagnosed myasthenia gravis and the ensuing problems that developed. We also discuss the appropriate investigation and subsequent management of such patients and the pitfalls in train-of-four (TOF) monitoring.

Case report

A 43-yr-old, 95 kg, female (ASA class I) presented for laparoscopic cholecystectomy and intra-operative cholangiogram. The patient had no significant past medical history, took no regular medications and had undergone two uneventful general anaesthetics for open reduction and internal fixation of her right ankle in 1993, with subsequent removal of pins in 1994. She did not smoke nor drink alcohol. Pre-operative investigations (full blood count, urea and electrolytes, coagulation studies, liver function tests, chest x-ray, and electrocardiograph) were normal.

In the anaesthetic room, i.v. access was obtained and in addition to routine monitoring a forced air warming device was used. Anaesthesia was induced with propofol 200 mg and fentanyl 100 µg. Vecuronium 10 mg was given to facilitate tracheal intubation. Droperidol 0.5 mg was given as an anti-emetic and cefotetan 1 g as antibiotic prophylaxis. Anaesthesia was maintained with isoflurane 1.5% and nitrous oxide 50% in oxygen and the lungs were artifically ventilated. Morphine in increments up to 8 mg was given i.v. for analgesia. After 90 min of uneventful anaesthesia and surgery, neostigmine 2.5 mg and glycopyrrolate 0.4 mg were given to antagonize any residual neuromuscular block. The TOF ratio was checked using a Fischer Paykel 'Innervator' peripheral nerve stimulator with a current of 60 mA at the ulnar nerve after the reversal agents had been given. There was no fade evident by tactile estimation; the first and fourth twitches were apparently equal in size. Anaesthesia was discontinued and the patient allowed wake up. It quickly became obvious that the patient was having difficulty breathing (rapid shallow breaths) and the end-tidal carbon dioxide concentration (E'_{CO_2}) rose rapidly to 80 mm Hg with the trachea still intubated. Oxygen saturation remained at 97% throughout. At this time, the patient was unable to raise her head from the bed or to sustain a handgrip. The TOF ratio was re-checked and again no fade was evident by tactile means; a further dose of neostigmine 2.5 mg was given. (Although it would have been appropriate

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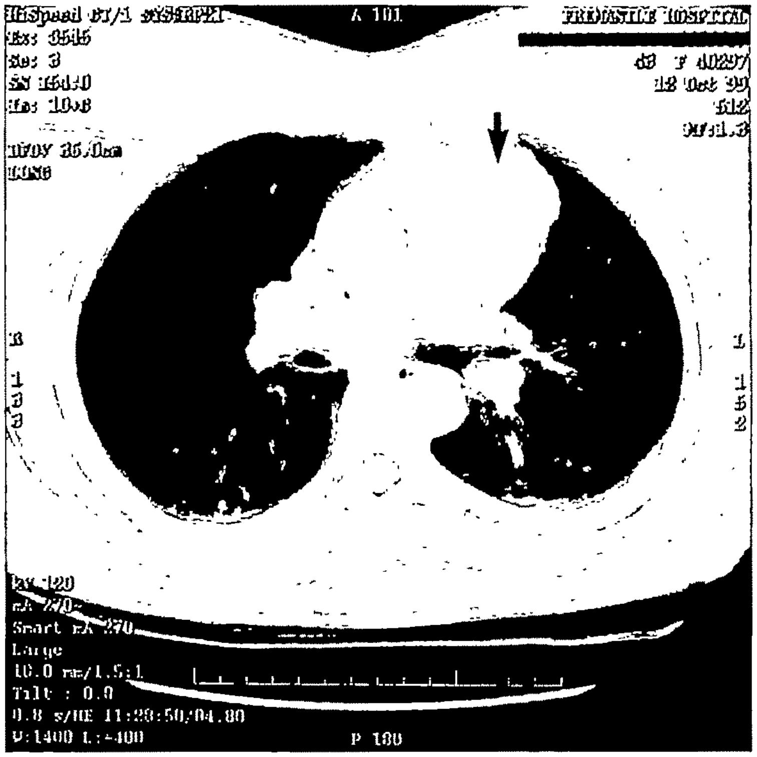

Fig 1 CT scan with i.v. contrast shows large thymoma (arrowed) anterior to the ascending arch of the aorta and right pulmonary artery.

to check for fade in the double burst stimulus at this time, the nerve stimulators with this capacity were being repaired and we were unable to do so.) There was no improvement in respiratory function over the next 10 min, so the patient was re-anaesthetized using propofol 100 mg.

A search for causes of inadequate respiratory effort commenced whilst anaesthesia was maintained. There was no clinical evidence of a pneumothorax. A suction catheter was easily passed down the tracheal tube; there was no airway obstruction, nor any evidence of aspiration. Electrolyte abnormalities were thought unlikely as the patient had normal renal and liver function pre-operatively. She had not been given any medication that would have interfered with neuromuscular transmission. Her pupils were mid size and she had only received morphine 8 mg. Her temperature was 35.8°C. The TOF was checked 25 min after the second dose of neostigmine with no tactile evidence of fade. At this stage, it was postulated that she might have an underlying neuromuscular disorder. Anaesthesia was maintained for a further 2 h until her ventilatory function had improved as assessed by an increase in tidal volume and a reduction in E'_{CO_2} to 45 mm Hg. The trachea was successfully extubated 2.5 h after the end of surgery. The patient was monitored for a further 3 h in the recovery room where it became obvious that she had generalized muscle weakness as evidenced by her limited ability to raise her head from the bed or to sustain a handgrip for 5 s. She was discharged to the ward that evening where she remained stable overnight.

The patient was re-interviewed the next morning when she admitted that she had been attending her general practitioner for the past 18 months complaining of symptoms of tiredness, occasional hoarse voice (for which she had seen a speech therapist), difficulty chewing, and occasional slurred speech. On further questioning she also admitted to having problems hanging out her washing because of easily fatigued arms and being unable to rise from a squatting position. This information was not volunteered at the original anaesthetic consultation as the patient's general practitioner had told her these symptoms were nothing to worry about and she had dismissed them as unimportant. On examination, she had weakness of her facial muscles, neck extensors, and fatigable proximal weakness of both upper and lower limbs. There were no sensory abnormalities.

The case was discussed with the neurologists who felt that the most likely diagnosis was myasthenia gravis. The 'Tensilon test' was positive after edrophonium 5 mg given i.v. Repetitive nerve conduction studies were negative. Plasma acetylcholine receptor antibody (AchR) levels were 4.3 local units (normal range <0.1). Computerized tomography (CT) of the mediastinum (Fig. 1) showed a large anterior mass compatible with a thymoma despite the chest x-ray being normal. Thyroid function tests were normal. A search was made for coincidental autoimmune disease but this proved negative.

These results confirmed the clinical diagnosis of myasthenia gravis. The patient was discharged home on

Table 1 Osserman and Genkins classification of disease severity[5]

Grade 1	Ocular disease only
Grade 2A	Generalized muscle weakness with ocular symptoms
Grade 2B	Generalized moderate weakness and/or bulbar dysfunction
Grade 3	Acute fulminating presentation and/or respiratory dysfunction
Grade 4	Late severe generalized disease

no treatment. The patient underwent an uneventful thymectomy 4 weeks later. Histological examination proved this to be a benign thymoma. This time she had an uneventful general anaesthetic using propofol, alfentanil, oxygen, nitrous oxide, isoflurane, and morphine. No neuromuscular blocking drugs were used. The trachea was extubated at the end of the procedure. She was managed uneventfully on the ward post-operatively.

Discussion

The incidence of myasthenia gravis is 1 in 10 000–20 000 adults.[3] The hallmark of the disease is weakness and rapid fatigability of voluntary skeletal muscles with repetitive use followed by partial recovery with rest.[3] The muscular disorder is generalized in 85% of patients and confined to the extra-ocular muscles in 15%. Extremity musculature is symmetrically affected with weakness of proximal muscle groups preferentially involved. Myasthenia gravis occurs in a bimodal age distribution. It occurs predominantly in women in their twenties and thirties and in men in their sixties and seventies. The mean age of onset is 26 yr.[4] Overall, women are more commonly affected than men in the ratio 3:2. The disease is graded using the Osserman and Genkins staging classification (Table 1);[5] our patient fell into category 2A with her mild generalized weakness.

Approximately 10% of patients with myasthenia gravis have an associated autoimmune disorder. These include hyper- or hypothyroidism, which may exacerbate symptoms or masquerade as myasthenia gravis itself. Rheumatoid arthritis and systemic lupus erythematosis present their own problems respectively.

Myasthenia gravis results from production of autoantibodies against the nicotinic AchR at the neuromuscular junction which reduces the number of functioning receptors either by competitive block, increased degradation of receptors or by complement mediated lysis of receptors.[6] In general, myasthenics have one-third as many normally functioning AchRs as those who are disease free. In normal individuals, repetitive nerve stimulation results in a decrease in the amount of Ach released with each successive stimulus. Drachman[7] refers to this as 'rundown'. The combination of less neurotransmitter release and fewer receptor sites leads to muscular weakness in myasthenics. It has long been appreciated that there is a relationship between the thymus and myasthenia gravis[8] with the three commonest abnormalities being hyperplasia, thymoma (benign or malignant) and atrophy. Thymomas are more common in patients over 30 yr whereas hyperplasia is commoner in younger age groups. There is a consensus that all adults with generalized myasthenia gravis should have a thymectomy as this improves symptoms, reduces or abolishes the need for drugs and can induce long-lasting remission. Currently quoted figures are clinical improvement in 78–96% and drug free remission in 42–69%.[9]

The 'Tensilon test' is a simple first line test for myasthenia gravis. Edrophonium (Tensilon), a short-acting anticholinesterase, is administered i.v. in doses of 2–10 mg and an improvement in muscle strength is expected. It is said to be positive in 95% of those with myasthenia gravis. It is least sensitive in patients with ocular symptoms alone. It also has a low specificity. False positive tests occur in patients with other neurological disorders such as amyotropic lateral sclerosis or Lambert–Eaton myasthenic syndrome. Performing it after the patient has exercised when the weakness is maximal may increase the sensitivity of the test. Repetitive nerve stimulation involves stimulating a peripheral nerve at 2–3 Hz and recording the resulting action potential via surface electrodes over the target muscle. A decrease of 15% in successive action potentials is considered positive. The test is safe and simple but is insensitive and may not be positive in up to 50% of patients especially those with mild disease. AchR antibody assay detects antibodies in 80–90% of patients with myasthenia gravis. However, detection rates may be as low as 50% in those with mild disease.[4] Single fibre electromyography requires experienced personnel, is expensive and is seldom used. As in this patient, CT scanning of the mediastinum is used to visualize the anterior mediastinum for evidence of thymoma.

The other issue of importance well illustrated by this case is the inaccuracy of tactile measurement of the TOF ratio. On the first occasion it was performed, a consultant anaesthetist observed it and on second and subsequent times a consultant and senior registrar observed it. Our interpretation of the TOF ratio was clearly inaccurate. It was obvious, clinically, that the patient had residual neuromuscular block despite the absence of visible fade in the TOF ratio. Recent studies would appear to support our finding that it is not possible to exclude significant residual paralysis by visual or tactile evaluation of the TOF ratio,[10 11] and that even experienced anaesthetists are unable to feel fade if the TOF ratio has recovered to 0.4 or greater.[11 12] Unfortunately, double-burst stimulation (DBS) was not performed in this patient, as the nerve stimulator did not have the facility for this function. Perhaps if we had been able to perform this test, fade would have been more evident as it is easier to demonstrate fade in DBS than the TOF.[13]

It has been stated that a TOF ratio of $\geqslant$0.7 measured at the thumb is compatible with adequate neuromuscular recovery.[14] Recent studies, however, have confirmed that a TOF ratio of 0.7 does not guarantee adequate recovery of neuromuscular function and at this TOF ratio chemoreceptor sensitivity to hypoxia is reduced,[15 16] further reducing the stimulus to breathe. It has also been shown that at this

TOF ratio the muscles of the upper oesophagus and pharynx show functional impairment, thus predisposing to regurgitation and aspiration.[17] Accordingly it as been stated that normal vital function and normal pharyngeal function requires a TOF ratio of ⩾0.9.[18 19]

On all occasions, there was no fade evident despite two doses of neostigmine (2.5 mg each) being given. There is some debate of the value of a second dose of neostigmine. Work published some years ago suggested that a second dose of neostigmine 2.5 mg, given 2–5 min after a first dose, could lead to a neostigmine-induced block in normal patients.[20] However the neuromuscular blocking drugs being antagonized in that study (tubocurarine, dimethyltubocurarine, gallamine) are no longer in clinical use. More recent work demonstrated that two doses of neostigmine 2.5 mg, given 2 min apart to normal patients recovering from atracurium-induced neuromuscular block, were no more effective than one dose. However, there were no reports of neostigmine-induced block.[22] Work by Hunter[22] in a series of myasthenics receiving vecuronium, also confirmed that a second dose of neostigmine 2.5 mg given 5 min after the first conferred no additional benefit.

It has been suggested that more objective methods such as accelerography, mechanomyography or electromyography,[23] be used if there is any doubt about possible residual block. However, these techniques are expensive, impractical and most departments do not possess them. Perhaps the simplest way to avoid post-operative residual curarization is to monitor all patients who receive neuromuscular blockers with DBS at regular intervals throughout anaesthesia. It is imperative to appreciate that reliance on TOF monitoring using visual or tactile methods to assess residual neuromuscular block is at best inaccurate and at worst dangerous.

References

1 Eisencraft JB, Brook WJ, Papatestas AE. Sensitivity to vecuroniun in myasthenia gravis: a dose response study. *Can J Anaesth* 1990; **37**: 301–6

2 Buzello W, Noeldge G, Kreig N, Brobmann GF. Vecuronium for muscle relaxation in patients with myasthenia gravis. *Anesthesiology* 1986; **64**: 507–09

3 Drachman DB. Myasthenia gravis. *N Engl J Med* 1978; **298**: 136–42

4 Heitmiller RF. Myasthenia gravis: clinical features, pathogenesis, evaluation and medical management. *Semin Thorac Cardiovasc Surg* 1999; **11**: 41–6

5 Osserman KE, Genkins G. Studies on myasthenia gravis. Review of a twenty year experience in over 1200 patients. *M Sinai J M* 1971; **38**: 497–537

6 Krucylak PE, Naunheim KS. Preoperative preparation of and anaesthetic management of patients with myasthenia gravis. *Semin Thorac Cardiovasc Surg* 1999; **11**: 47–53

7 Drachman DB. Myasthenia gravis. *N Engl J Med* 1994; **330**: 1797–1810

8 Hohlfield R, Wekerele H. The thymus in myasthenia gravis. *Neurol Clin* 1994; **12**: 331–40

9 Heitmiller RF, Heitmiller ES. Surgery for myasthenia gravis. In: Franco KL, Putman J, eds. *Advanced Therapy in Thoracic Surgery*. Philadelphia, PA: B. C. Decker, 1998; 423–31

10 Pederson T, Viby-Mogenson J, Bang U; Olsen NV, Jensen E, Engbaek J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative neuromuscular blockade? *Anesthesiology* 1990; **73**: 835–9

11 Viby-Mogenson J, Jensen NH, Engbaek J, Ording H, Skovgard LT, Chaemmer-Jorgensen B. Tactile and visual evaluation of response to train-of-four nerve stimulation. *Anesthesiology* 1985; **63**: 440–3

12 Saddler JM, Bevan JC, Donati F, Bevan DR, Pinto MB. Comparison of double-burst and train-of-four stimulation to assess neuromuscular blockade in children. *Anesthesiology* 1990; **73**: 401–3

13 Drenk NE, Ueda N, Olsen NV, *et al.* Manual evaluation of residual curarisation using double burst stimulation. A comparison with train-of-four. *Anesthesiology* 1989; **70**: 578–81

14 Ali HH, Utting JE, Gray TC. Quantitative assessment of reversal of antidepolarising block (part II). *Br J Anaesth* 1971; **43**: 478–85

15 Eriksson L, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium induced partial neuromuscular block. *Acta Anaesthesiol Scand* 1992; **36**: 710–15

16 Eriksson LI, Sato M, Servinghus JW. Effect of a vecuronium induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology* 1993; **78**: 693–9

17 Eriksson LI, Sundman E, Olsson R, *et al.* Functional assessment of the pharynx at rest and during swallowing in partially paralysed humans. *Anesthesiology* 1997; **87**: 1035–43

18 Kopman AF, Yee PS, Neuman GG. Relationship of the train of four ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology* 1997; **86**: 765–71

19 Eriksson L. The effects of residual neuromuscular blockade and volatile anaesthetics on the control of ventilation. *Anesthesiology* 1999; **89**: 243–51

20 Payne JP, Hughes R, Al Azawi S. Neuromuscular blockade by neostigmine in anaesthetised man. *Br J Anaesth* 1980; **52**: 69

21 Fox MA, Keens J, Utting JE. Neostigmine in antagonism of the action of atracurium. *Br J Anaesth* 1987; **59**: 468–72

22 Hunter JM, Bell CF, Florence AM, Jones RS, Utting JE. Vecuronium in the myasthenic patient. *Anaesthesia* 1985; **40**: 848–53

23 Mortenson CR, Berg H, El-Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using accelerography prevents residual muscular block following pancuronium. *Acta Anaesthesiol Scand* 1995; **39**: 797–801

British Journal of Anaesthesia **86** (5): 731–3 (2001)

Haemodynamic changes during retroperitoneoscopic adrenalectomy for phaeochromocytoma

F. Atallah[1]*, T. Bastide-Heulin[1], M. Soulié[2], F. Crouzil[1], A. Galiana[1], K. Samii[1] and C. Virenque[1]

[1]Department of Anaesthesiology and [2]Department of Urology, Rangueil Hospital, Toulouse University Hospitals, F-31403 Toulouse Cedex 4, France

**Corresponding author*

Surgical removal of phaeochromocytoma may be accompanied by acute cardiovascular changes. We report the haemodynamic changes in seven patients with retroperitoneal laparoscopic adrenalectomy for phaeochromocytoma. Transient hypertension (systolic pressure (SBP) >160 mm Hg) was observed in all patients during manipulation of the tumour, in two patients during pneumoretroperitoneum insufflation, and in one patient during intubation. Small doses of nicardipine were sufficient to control these episodes of hypertension. Transient hypotension (SBP <100 mm Hg) was observed in two patients during exsufflation and in one patient during repositioning to the lateral position. Our observations suggest that this approach provides relative haemodynamic stability, especially during pneumoretroperitoneum insufflation.

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Keywords: phaeochromocytoma; cardiovascular system, responses; measurement techniques, retroperitoneoscopy

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Surgical removal of adrenal phaeochromocytoma may be accompanied by severe and acute haemodynamic changes.[1] The laparoscopic approach allows more gentle manipulation of the tumour and direct access to the adrenal vein, resulting in less catecholamine release. Production of a pneumoperitoneum is, however, known to induce haemodynamic changes and catecholamine release.[2]

Retroperitoneal laparoscopy has some advantages compared with transperitoneal laparoscopy. It causes only a small increase in intra-abdominal pressure and fewer haemodynamic changes.[3] It facilitates early clipping of the adrenal vein by direct retroperitoneal access to the vessels.

No previous study has reported the haemodynamic changes during retroperitoneal laparoscopy for phaeochromocytoma. We report them in seven such patients.

Case reports

Seven consecutive patients with a clinical and laboratory diagnosis of phaeochromocytoma were studied retrospectively. The diagnosis of phaeochromocytoma was confirmed histologically in all patients post-operatively. Retroperitoneoscopic adrenalectomy was done through a lateral approach, by the same surgeon. Patient characteristics and anaesthetic management are shown in Table 1.

All patients were treated for 7–10 days pre-operatively with labetalol 150–400 mg orally, to stabilize the arterial pressure (<150/90 mm Hg) and the heart rate (<100 beats min^{-1} and regular). Labetalol was given on the morning of surgery and patients were pre-medicated with oral flunitrazepam 2 mg. Radial artery cannulation was performed under local anaesthesia. General anaesthesia was induced by i.v. midazolam 5 mg, sufentanil 0.5 µg kg^{-1} and either propofol 2 mg kg^{-1} or etomidate 0.25 mg kg^{-1}. Tracheal intubation was facilitated with a non-depolarizing neuromuscular blocking drug. Anaesthesia was maintained with isoflurane or desflurane (MAC 0.6–0.8), sufentanil 0.2–0.5 µg kg^{-1} h^{-1} and a continuous infusion of a non-depolarizing neuromuscular blocking drug (Table 1). Patients were mechanically ventilated with nitrous oxide 50% in oxygen, at a tidal volume of 10 ml kg^{-1}. Ventilatory rate was adjusted to keep $P\acute{E}_{CO_2}$ between 4.0 and 4.8 kPa. If needed, either nicardipine (starting with 2 mg h^{-1}) or norepinephrine (starting with 1 mg h^{-1}) was administered by continuous infusion to maintain a systolic pressure (SBP) between 120 and 160 mm Hg. Esmolol 0.5 mg kg^{-1} was used if heart rate exceeded 100 beats min^{-1}.

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Table 1 Patient characteristics, anaesthetic management, arterial pressure changes and doses of hypertensive and hypotensive drugs used. Ep, epinephrine; Norep, norepinephrine; F, female; M, male; ↑=systolic hypertension; ↓=systolic hypotension. *Patient 7 developed palpable subcutaneous emphysema resulting in a moderate refractory hypercapnia

Patient	Age (yr)	Sex	Side	Tumour production	Pre-operative symptoms	Halogenated anaesthetic	Neuromuscular blocking drug	Arterial pressure changes	Drugs used
1	23	F	left	Norep	present	Isoflurane	atracurium	insufflation: ↑ tumour manipulation: ↑ exsufflation: ↓	nicardipine =2.5 mg nicardipine =1.5 mg norep =3.2 mg
2	48	M	left	Ep+Norep	present	isoflurane	atracurium	changing position: ↓ tumour manipulation: ↑	norep =0.4 mg nicardipine =4 mg
3	48	M	left	Ep+Norep	absent	isoflurane	vecuronium	insufflation: ↑ tumour manipulation: ↑	nicardipine =2 mg nicardipine =10 mg
4	48	M	right	Ep+Norep	absent	desflurane	vecuronium	intubation: ↑ tumour manipulation: ↑ exsufflation: ↓	nicardipine =1.5 mg nicardipine =25 mg norep =0.6 mg
5	39	F	right	Norep	absent	isoflurane	vecuronium	tumour manipulation: ↑	nicardipine =5 mg
6	17	M	left	Ep+Norep	present	desflurane	cisatracurium	tumour manipulation: ↑	nicardipine =2.25 mg
7*	31	F	right	Ep	present	desflurane	cisatracurium	tumour manipulation: ↑	nicardipine =15.0 mg

After induction, a central vein was cannulated. Patients were then placed in the lateral position. Retroperitoneal insufflation with carbon dioxide was maintained with a pressure between 12–14 mm Hg. The duration of surgery varied between 100 and 255 min (mean 171 (SD 60) min) and that of anaesthesia varied between 195 and 360 min (269 (70) min). This difference is explained by the time needed to cannulate a central vein and the position changes of the patient. Patients received 2600 (450) ml of lactated Ringer's solution and 710 (270) ml of hydroxyethyl starch solution (colloid); no blood transfusion was needed.

Transient hypertension (SBP >160 mm Hg) was observed in all patients during manipulation of the tumour, in two patients during pneumoretroperitoneal insufflation and in one patient during intubation. Small doses of nicardipine (bolus of 1–2 mg, followed by infusion of 2–6 mg h^{-1}) were sufficient to control these episodes of hypertension. Transient hypotension (SBP <100 mm Hg) was observed in two patients during exsufflation and in one patient during repositioning to the lateral position. No arrhythmia or tachycardia (>100 beats min^{-1}) was observed in any patient (Fig. 1A and B).

Discussion

When we were first undertaking adrenalectomy for phaeochromocytoma using the retroperitoneal laparoscopic approach, we expected more haemodynamic disturbances than that reported with the transperitoneal approach; we predicted greater carbon dioxide absorption. But we rapidly noticed haemodynamic stability with this technique.

In this case-series, manipulation of the tumour was the only event consistently associated with hypertension (Fig. 1). In a report of eight patients undergoing laparoscopic transperitoneal adrenalectomy for phaeochromocytoma, Joris and colleagues observed two causes of significant hypertension: creation of the pneumoperitoneum and adrenal gland manipulation.[2]

Retroperitoneal laparoscopy produces only a small increase in intra-abdominal pressure; Chiu and colleagues[3] reported an increase of 3 mm Hg. This difference may explain the relative haemodynamic stability we observed during insufflation. With retroperitoneoscopy, there is little stimulation of the peritoneum and, hence, less sympathetic response and less catecholamine release.

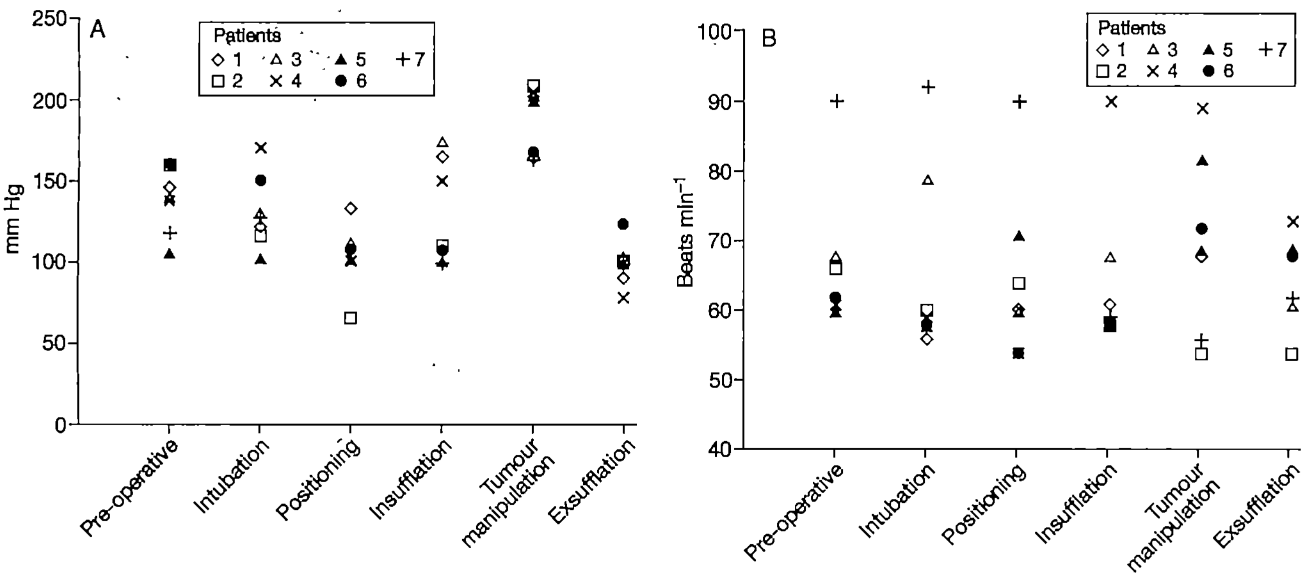

Fig 1 (A) Pre-operative systolic pressure changes (mm Hg). (B) Pre-operative heart rate changes (beats min^{-1}).

There is still some controversy concerning whether retroperitoneoscopy produces more[4 5] or less[6 7] carbon dioxide absorption than i.p. laparoscopy. Ng and colleagues recently demonstrated that the retroperitoneal approach produces the same or even less hypercapnia, provided that insufflation is limited to the retroperitoneal space.[8] This can be explained by the larger absorptive area available in the peritoneal cavity and the greater absorptive capacity of the peritoneal membrane.[9] Furthermore, operating on a retroperitoneal viscera by transperitoneal laparoscopy allows systemic carbon dioxide absorption from both the peritoneal cavity and the retroperitoneal areas.

Subcutaneous emphysema remains a common complication of retroperitoneal laparoscopy with a reported incidence of 45%.[8] In our report, palpable surgical emphysema developed in patient 7 causing a refractory hypercapnia (Pa_{CO_2}=6.0–6.4 kPa), despite doubling of the minute ventilation. This was not accompanied by any haemodynamic changes.

Operative time is decreasing with this teams' experience. We recently reported a mean time of 135 min in 52 retroperitoneal laparoscopic adrenalectomies.[10]

Phaeochromocytoma is rare and although this report concerns a small number of patients, we reviewed the effect of the following possible predictive factors on haemodynamic instability: pre-operative degree and type of catecholamine excretion; size and side of the adrenal tumour; presence and severity of pre-operative symptoms; and choice of the halogenated anaesthetic. None of these factors seems to predict the incidence or the importance of the haemodynamic changes.

Our observations in seven patients suggest that retroperitoneal laparoscopy is a valuable technique for adrenalectomy, resulting in relatively good haemodynamic stability in patients with phaeochromocytoma.

A prospective, randomized comparative study between the two approaches, transperitoneal and retroperitoneal, is needed to confirm these findings. This may, however, be difficult because of the rarity of these cases and the satisfaction of our surgical and anaesthetic team with this new approach.

References

1 Prys-Roberts C. Phaeochromocytoma—recent progress in its management. *Br J Anaesth* 2000; **85**: 44–57
2 Joris JL, Hamoir EE, Hartstein GM, *et al.* Hemodynamic changes and catecholamine release during laparoscopic adrenalectomy for pheochromocytoma. *Anesth Analg* 1999; **88**: 16–21
3 Chiu AW, Chang LS, Birkett DH, Babayan RK. The impact of pneumoperitoneum, pneumoretroperitoneum, and gasless laparoscopy on the systemic and renal hemodynamics. *J Am Coll Surg* 1995; **181**: 397–406
4 Wolf JS, Monk TG, McDougall EM, McClennan BL, Clayman RV. The extraperitoneal approach and subcutaneous emphysema are associated with greater absorption of carbon dioxide during laparoscopic renal surgery. *J Urol* 1995; **154**: 959–63
5 Mullet CE, Viale JP, Sagnard PE, *et al.* Pulmonary CO_2 elimination during surgical procedures using intra- or extraperitoneal CO_2 insufflation. *Anesth Analg* 1993; **76**: 622–6
6 Bannenberg JJ, Rademaker BM, Froeling FM, Meijer DW. Hemodynamics during laparoscopic extra- and intraperitoneal insufflation. An experimental study. *Surg Endo* 1997; **11**: 911–5
7 Wolf JS, Carrier S, Stoller ML. Intraperitoneal versus extraperitoneal insufflation of carbon dioxide gas for laparoscopy. *J Endourol* 1995; **9**: 63–6
8 Ng CS, Gill IS, Sung G, Whalley DG, Graham R, Schweizer D. Retroperitoneoscopic surgery is not associated with increased carbon doxide absorption. *J Urol* 1999; **162**: 1268–72
9 Collins J. Inert gas exchange of subcutaneous and intraperitoneal gas pockets in piglets. *Respir Physiol* 1981; **46**: 391
10 Soulie M, Mouly P, Caron P, *et al.* Retroperitoneal laparoscopic adrenalectomy: Clinical experience in 52 procedures. *Urology* 2000; **56**: 921–5

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Correspondence

Conflicts of interest: are they a problem for anaesthesia journals?

Editor—Dr Sneyd writes convincingly concerning conflicts of interest,[1] arguing for a greater disclosure that all leading anaesthesia journals could agree to. I thank him for his several references to our work but prefer that the work not be characterized as a 'crusade against sevoflurane'. First, of the 42 articles suggested as part of that crusade, several do not detract from sevoflurane (e.g. measuring its partition coefficients in tissues[2] and plastics,[3] comparing its kinetics to those of isoflurane,[4] defining its neuromuscular properties,[5] showing that it does not predispose to arrhythmias,[6] providing values for its density,[7] finding that it is not degraded to carbon monoxide,[8] and more). Second, we concurrently reported potentially negative aspects of desflurane (e.g. defining the dose-response relationships leading to tachycardia and hypertension,[9,10] discovering that absorbent desiccation causes carbon monoxide production from desflurane,[8] showing that propofol fails to attenuate the cardiovascular response to rapid increases in desflurane concentration,[11] and more), but these are not part of a 'crusade against desflurane'. Third, our 42 articles (out of nearly 200 articles written over the same period of time) are outnumbered by those of investigators 'defending' sevoflurane (e.g. T Ebert, E Kharasch, and R Mazze). I do not (nor, I think, would Dr Sneyd) characterize their work as a 'crusade for sevoflurane' (but can we start a trend?).

If not 'crusade', what? 'Passion' or 'an abiding interest' or 'dedication to/ownership of an idea' perhaps. As Sneyd noted, these can be more potent sources of bias than financial conflict of interest.[12] And they cannot be revealed by disclosures of connections to commercial enterprises. We rely on the reviewers of submitted articles to prevent passion and interest from compromising objectivity.

Sneyd's essay gently echoes Dr Saidman's sentiment[13] that those with ties to commercial enterprises (e.g. Eger) should avoid research that deals with the products of these enterprises, delegating such research to independent (objective? dispassionate?) investigators. Although delegation eliminates the financial conflict of interest, it comes at a price. Show me an independent, objective, dispassionate investigator, and I will show you an uninterested investigator. I am open to increased disclosure, but we do the anaesthesia community a disservice if we take passion from research.

E.I. Eger
San Francisco
USA

1 Sneyd JR. Conflicts of interest: are they a problem for anaesthesia journals? What should we do about them? *Br J Anaesth* 2000; **85**: 811–4

2 Strum DP, Eger EI, II. Partition coefficients for sevoflurane in human blood, saline, and olive oil. *Anesth Analg* 1987; **66**: 654–6

3 Targ AG, Yasuda N, Eger EI, II. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. *Anesth Analg* 1989; **68**: 218–25

4 Yasuda N, Lockhart SH, Eger EI, II, Weiskopf RB, Liu J, Laster M, Taheri S, Peterson NA. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991; **72**: 316–24

5 Shin Y-S, Miller RD, Caldwell JE, Eger EI, II. The neuromuscular effects of sevoflurane and isoflurane alone and in combination with vecuronium or atracurium in the rat. *J Anesth* 1992; **6**: 1–8

6 Navarro R, Weiskopf RB, Moore MA, Lockhart S, Eger EI, II, Koblin D, Lu G, Wilson C. Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic responses to epinephrine. *Anaesthesiology* 1994; **80**: 545–9

7 Laster MJ, Fang Z, Eger EI, II. Specific gravities of desflurane, enflurane, halothane, isoflurane and sevoflurane. *Anesth Analg* 1994; **78**: 1152–3

8 Fang ZX, Eger EI, II, Laster MJ, Chortkoff BS, Kandel L, Ionescu P. Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme®. *Anesth Analg* 1995; **80**: 1187–93

9 Weiskopf RB, Moore M, Eger EI, II, *et al.* Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. *Anesthesiology* 1994; **80**: 1035–45

10 Weiskopf RB, Eger EI, II, Noorani M, Daniel M. Repetitive rapid increases in desflurane concentration blunt transient cardiovascular stimulation in humans. *Anesthesiology* 1994; **81**: 843–9

11 Daniel M, Eger EI, II, Weiskopf RB, Noorani M. Propofol fails to attenuate the cardiovascular response to rapid increases in desflurane concentration. *Anesthesiology* 1996; **84**: 75–80

12 Horrobin DF. Beyond conflict of interest. Non-financial conflicts of interest are more serious than financial conflicts. *Br Med J* 1999; **318**: 466

13 Saidman LJ. Motivation, bias, and scientific integrity. *Anesthesiology* 1994; **81**: 271

Skin testing and the anaesthetist

Editor—It gave me great pleasure to see my friend and sparring partner, John Watkins, re-entering the lists in his editorial on skin testing and the anaesthetist.[1]

There was one important error of fact in the editorial. It stated that 'most reactors have evidence of previous uneventful exposure to that drug and hence some sort of conventional immune sensitization'. For the neuromuscular-blocking drugs (NMBDs) this is not supported by the literature. The highest incidence of previous exposure to the same muscle relaxant was 45%, described by Galletly and Trueran.[2] The current data from our own series is shown in Table 1. I confess that in recent years I have not pursued previous anaesthetic records with the vehemence I did in past years, but the figures are constant and supported by other series. In 1974 we began research on this topic particularly

Table 1 Previous exposure in patients with severe anaphylactic reactions to muscle relaxants

Drug	Patients	Previous exposure		
		Yes	No	Unknown
Succinylcholine	134	25	65	44
Alcuronium	129	31	72	26
Atracurium	41	2	34	4
Rocuronium	33	2	26	5
D-tubocurarine	23	2	16	5
Vecuronium	19	0	11	8
Gallamine	17	2	12	3
Pancuronium	13	0	8	5
Cisatracurium	2	0	2	0
Mivacurium	1	0	1	0
Decamethonium	1	0	1	0
	413	64	248	100

to find out what sensitized people to NMBDs. It is a tribute to my abilities as a researcher that 26 years later I have no idea! I suspect that a clue may lie in the apparent different incidences of allergy to NMBDs in different countries. Anaphylaxis to NMBDs seems extremely rare in the United States, South Africa and Scandinavia and very much more common in Europe, Australia and New Zealand.

I would further suggest that it may be that previous exposure to an anaphylactic culprit NMBD is coincidental and not an exposure which leads to the formation of antibodies. It is difficult to conceive how a molecule as simple as succinylcholine, for example, could lead to sensitivity many years later after a single exposure. These data are not purely of academic interest. If it were as Dr Watkins suggests, one could exclude relaxants used for the first time as causes of an anaphylactic reaction. There would be no need to test for these relaxants. The consequences could be disastrous both for patient and probably anaesthetist.

I would take issue with another two of Watkins' remarks. I am sure that we both agree that it is of great value to have special units which take an interest in investigating anaphylactoid and anaphylactic reactions during anaesthesia. But I do not share his preference for dermatologists or allergologists as the key players, and our own experience suggests that even a 'one-off investigation by an anaesthetist' is preferable. The reasons are simple. When life-threatening adverse reactions occur during anaesthesia, an anaphylactic cause is the only one that can be proven. Thus, virtually any other potential cause is critically dependent on the interpretation of the clinical description of the event. Other causes are more likely, and their aetiology is most likely to be found by an experienced anaesthetist. An allergologist or immunologist with an interest in such reactions is a highly prized individual to be nurtured. Outside of France, however, few have emerged. A significant number of the patients at our clinic are referred by allergists, and a significant number referred by anaesthetists after being seen by allergists. The subject does not seem well taught.

Watkins also believes it is 'a current unsatisfactory trend to test simultaneously a panel of all the usual NMBDs with a view to elucidating future potential cross re-activity'. While I agree that the same dilution for all the drugs is not appropriate and certainly 'neat ampoule strength' should not be used, I believe that such investigation is mandatory. There is a 60% incidence of cross-sensitivity between muscle relaxants. The aims of investigations in these patients are twofold. One aim is to determine the cause of the reaction that injured the patient. The second (and more important aim) is to make the next anaesthetic safe. There is now good data from several independent groups that show that if all drugs which are skin-test positive are avoided, subsequent anaesthesia with skin-test negative drugs is more likely to be safe than if positive drugs are used. There are sufficient correlations now with radioimmunoassay tests and in patients who have reacted to more than one NMBD on separate occasions to support this practice, which is usually but not invariably safe.[3] The compromise in availability for future anaesthesia is something that we should be prepared to accept in the interests of safety.

Watkins calls for clear, rationally agreed guidelines on the investigation of hypersensitivity-type reactions. I endorse this wholeheartedly and the Association of Anaesthetists in Great Britain and Ireland can be congratulated for the documents they have produced on this which I believe still provide a valid approach. The other day I was consulted by a horrified orthopaedic surgeon who had been about to inject a drug into a patient's vertebral disc. Due to the incidence of anaphylaxis to this drug, a pre-operative testing kit was provided. The orthopaedic surgeon was perturbed by the instructions to 'place one drop of each solution on the patient's forearm and prick'.

M. Fisher
Intensive Therapy Unit
Royal North Shore Hospital of Sydney
Sydney
Australia

1 Watkins J. Skin testing and the anaesthetist. *Br J Anaesth* 2000; **85**: 814–6

2 Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33

3 Fisher MM, Merefield D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999; **82**: 770–3

Editor—It was nice to read the comments on my editorial from my old friend Professor Malcolm Fisher: in the past our public exchanges were considered entertaining. It must be a sign of increasing age that I find much to agree with in his comments.

However, Malcolm's principal objection was to my statement that most reactors have evidence of previous uneventful exposure leading to the surmise of conventional immune sensitization. I am aware of the evidence to the contrary, but the statement was based on 25 years of my own UK experience. Clearly, life threatening adverse response can occur on first exposure and equally clearly, if the investigator uses too high a test concentration of the drug(s), he or she will produce a convincing weal and flare response. This is extremely easy to do with the benzylisoquinolines and also with rocuronium, as Levy has demonstrated.[1] Whether or not these represent genuine immune, antibody-mediated responses, depends on the demonstration of 'explosively' high levels of plasma tryptase at the time of the reaction (i.e. acute mast cell degranulation). Moderately raised levels due to other underlying pathology, inflammatory response and the like, are readily excluded from a study of the case history and by experience. I believe that this procedure is used now by all key workers in the field and certainly by the Fisher and Laxenaire groups.

Using the combination of high plasma tryptase release and a 'positive' skin test I again confirm that, in my own experience, proven absence of previous exposure to the NMBA in a characterized immune response was uncommon and even then predominantly confined to succinylcholine reactions. Perhaps I should use my retirement to sort out and publish my old records. I do share Professor Fisher's views that the anaesthetist must always remain in control of the investigation. Few allergologists, dermatologists, or immunologists have a sufficient grasp of the complex pharmacology associated with modern anaesthesia. Nevertheless they have more experience in the limitations of the various *in vivo* and *in vitro* tests. While I can share a similar anecdotal allergologist's advice to that reported by Fisher, I have also encountered some pretty awful conclusions drawn by anaesthetists going it alone.

J. Watkins
Cawood
York, UK

1 Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; **85**: 844–9

Lobectomy for cavitating lung abscess

Editor—We read the interesting case report[1] involving placement of a double-lumen tube (DLT) and management of anaesthesia in a patient with a cavitating lung abscess. Although we are sure anaesthesia was well conducted in that patient, we disagree with some of the practices advocated.

First, in contrast to Pfitzner and colleagues,[1] and to avoid any contralateral spillover of pus in patients with a cavitating lung abscess, we avoid ventilation between induction and successful DLT intubation. To this end, we use a rapid sequence induction. Furthermore, having obtained CT-scans and chest X-rays, we do not see a great advantage of rigid bronchoscopy before intubation over fibreoptic bronchoscopy after successful DLT intubation in most patients with a cavitating abscess.

Second, we avoid a blind technique. We advocate using a fibrescope during intubation and inserting the bronchial limb into the left main bronchus under direct fibreoptic control. Alternatively, some of our colleagues place the left-sided tube in a blind manner, block the bronchial cuff and immediately perform fibreoptic bronchoscopy to ensure correct tube position before ventilating the patient. We strongly advocate using the fibrescope in controlling the position of the tube during or immediately following intubation because malposition may not be evident on auscultation[2]. Furthermore, auscultation may be misleading in patients with pathological processes in the lung. Malposition of the DLT may either lead to insufficient lung separation or to hypoxaemia. Both problems would require two-lung ventilation before lung separation is achieved, thus favouring cross-contamination. We believe that the fibrescope is not a last resort device, rather it is the control instrument of choice during and after intubation with a DLT.[2] We can only agree with a recent editorial in this journal advocating the use of fibrescope whenever a DLT is used.[3]

W. Karzai
U. Klein
Department of Anesthesiology and Intensive Care Therapy
University Hospital
Jena
Germany

1 Pfitzner J, Peacock MJ, Tsirgiotis E, Walkley ICH. Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung. *Br J Anaesth* 2000; **85**: 791–4
2 Klein U, Karzai W, Bloos F, *et al.* Role of fiberoptic bronchoscopy in conjunction with the use of double-lumen tubes for thoracic anesthesia: a prospective study. *Anesthesiology* 1998; **88**: 346–50
3 Pennefather SH, Russel GN. Placement of double lumen tubes—time to shed light on an old problem. *Br J Anaesth* 2000; **84**: 308–10

Editor—Thank you for the opportunity to comment on the letter of Drs Karzai and Klein. We must stress that the case report of anaesthesia for lung abscess[1] described our management of a patient who was at considerable risk of airway contamination with pus, blood or both. We discussed areas where other teams may well choose to adopt alternative strategies, and we even concluded that we would probably do it differently ourselves next time. For such a patient, we would seriously consider inducing anaesthesia prior to rigid bronchoscopy with the patient sitting on the edge of the horizontal lower half of an operating table that is broken at mid-point with the upper half of the table angulated steeply upwards. A sitting-reclining position, with the chest lying, abscess-side dependent, against the steeply angulated upper half of the table, is probably the most logical position for induction of anaesthesia in a patient with a cavitating lower lobe abscess.

We chose not to use the fibreoptic bronchoscope to assist double-lumen tube placement, although the instrument was immediately at hand throughout the operation. For reasons explained, we did not consider it necessary to check the tube position following placement. Instead, we focused our attention upon two separate aspects of management. First, maintaining uncomplicated single-lung ventilation of the 'good' lung and, second, refraining from ventilating the operated lung until after the lobectomy was complete and the airway cleared by endobronchial suction. Whereas Karzai and Klein may well be confident that following a rapid sequence induction they could reliably and promptly achieve fibreoptic-assisted lung separation in a patient placed in a semi-sitting position and with pus or blood possibly interfering with vision, we were not. However, we would not wish to criticize Karzai and Klein's preferred management plan simply because of our own personal experiences and preferences. Furthermore, we are confident that for such a patient they would have a back-up plan should fibreoptic-assisted double-lumen tube placement in the semi-sitting position prove difficult or prolonged.

J. Pfitzner
M.J. Peacock
The Queen Elizabeth Hospital Campus
North Western Adelaide Health Service
Adelaide, South Australia

1 Pfitzner J, Peacock MJ, Tsirgiotis E, Walkley IH. Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung. *Br J Anaesth* 2000; **85**: 791–4

Location of anaesthetic monitors

Editor—I welcome Nazir and Beatty's article on monitoring instrument design.[1] It looks at opinions of staff with regard to improving monitor design, in particular alarm notification. Morris and Montano looked at other aspects of monitoring, in particular response times to visual and audible alarms. They concluded that it is safer to rely on audible rather than visual alarms when time-critical information such as oxygenation, heartbeat and ventilator-disconnection is concerned. Visual alarms would appear to be more appropriate for conveying less urgent information. Westenskow and colleagues[3] looked at 'intelligent' monitors; in their study they asked anaesthetists to respond to breathing circuit problems. Human response time was 62% faster, decreasing from 45 to 17 s, when the intelligent alarm system was used. I agree with all these authors in that the premise of the articles was to seek out ways of improving safety.

I feel, however, that Nazir and Beatty may not have looked at a possibly crucial aspect of alarm and monitor design. This is the location of the monitor (or more accurately, the location of the integrated display unit). In most UK anaesthetic rooms and operating theatres, the display unit is placed on top of the anaesthetic machine above the eye level for most anaesthetists. The machine (and therefore the display unit) is behind the anaesthetist or is offset to their left or right. This arrangement is quite bewildering for the trainee when he/she first comes into theatre. At this stage, the anaesthetist is trying to keep their eyes on the display unit, watch the patient and see what the surgeons are doing (i.e. keep an eye on blood loss). What often happens is that one becomes the focus of attention to the detriment of the other. It is easy to see how the delays in response times to visual and audible alarms that have been documented can occur.

It would seem logical to me, in this digital age, to take advantage of the technology. Thin film transistor (TFT)[4] technology has improved vastly, such that small and study display units (say 10 inches across with a depth of no more than 2 inches) can be appointed on purpose-built stands, whose height can be adjusted (as in the manner of a drip stand) such that the monitor is set at a comfortable eye-level for the particular anaesthetist.

This is certainly feasible. We currently use Marquette© monitors in our hospital. We have 15 inch cathode ray tube displays in the operating theatre. We have small flat-panel TFT displays in the intensive care unit and for intra- and inter-hospital transfer of patients. During transfer, these are attached to a vertical bar within full view of the anaesthetists.

I feel that extending this 'simple' innovation into theatre will allow the trainee to watch the patient, the display unit, and the surgeon all at the same time. Further investigation in this area is warranted.

M. Nyabadza
Shackleton Department of Anaesthesia
Southampton General Hospital
Southampton, UK

1 Nazir T, Beatty PCW. Anaesthetists' attitudes to monitoring instrument design options. *Br J Anaesth* 2000; **85**: 781–4
2 Morris RW, Montano SR. Response times to visual and auditory alarms during anaesthesia. *Anaesth Intensive Care* 1996; **24**: 682–4
3 Westenskow DR, Orr JA, Simon FH, Bender HJ, Frankenberger H. Intelligent alarms reduce anesthesiologist's response time to critical faults. *Anesthesiology* 1992; **77**: 1074–9
4 'Thin Film Transistor active matrix displays'–ZDNet Website http://www.zdnet.com

Editor—Thank you for the opportunity to reply to Dr Nyabadza's letter concerning our paper.

Dr Nyabadza along with other authors,[1–3] is quite right to point out that the positioning of monitors in the average operating room is less than optimal and may well contribute to human factors' error. Probably the most radical solution suggested for this problem has been proposed by Block, Yablok and McDonald[4] who suggested using head-mounted displays to give anaesthetists a view of the monitoring displays wherever they look. As with Nyabadza's suggestion of using active matrix displays to improve the monitoring display position, as the unit cost of such technology falls, the possibility of using these or similar alternative methods will become easier.

However, even if the monitoring displays are positioned optimally within the field of view of the anaesthetist, there will remain fundamental issues of how and what to display on those monitors to make the displays as cognitively ergonomic as possible. In psychological terms, anaesthesia is in a class of safety-critical, cognitively complex problems that include flying aircraft or running a nuclear power plant. This means that the number of pieces of information that can be required to make a decision are more than the 5–8 that can be held in conscious working memory at one time. Thus, in a sense, the information visible on the monitoring display becomes an alternative memory of at least some of the information that the anaesthetist requires to make the next clinical decision. There is evidence that displays and alarms can make decision-making easier if they direct the attention of the user to the relevant information.[5] On the debit side, there is also evidence that fixation on displays contributes to the development of critical incidents in anaesthesia.[6] Thus the optimization of display design remains an important goal in improving the human factors' performance of monitoring equipment and therefore improving patient safety.

T. Nazir
P. Beatty
Manchester
UK

1 McIntyre J. Ergonomics: Anaesthetist' use of auditory alarms in the operating room. *Int J Clin Monitoring and Computing* 1985; **2**: 47–55
2 McIntyre J. Man-machine interface: the position of the anaesthetic machine in the operating room. *Can Anaesth Soc* 1982; **29**: 74–8
3 Boquet G, Bushman J, Davenport H. The anaesthesia machine—a study of function and design. *Br J Anaesth* 1980; **52**: 74–8
4 Block FE, Yablok DO, McDonald JS. Clinical evaluation of the "heads-up" display of anesthesia data. *Int J Clin Monitoring and Computing* 1995; **12**: 21–4
5 Woods DD. The alarm problem and directed attention in dynamic fault management. *Ergonomics* 1995; **39**: 237–93
6 DeAnda A, Gaba DM. Unplanned incidents during comprehensive anaesthesia simulation. *Anaesth Analg* 1990; **71**: 77–82

Electromyography and acceleromyography do not measure the same physiological event

Editor—We read with interest the article by Hemmerling and colleagues about the simultaneous determination of neuromuscular block at five different sites[1]. We congratulate the authors for their novel site for recording diaphragmatic responses after phrenic nerve stimulation.

Although we agree with the authors in their overall conclusion that the response to muscle relaxant drugs is different in different muscle groups, we do not agree with the method they used to reach this conclusion. To measure onset time and duration of mivacurium-induced neuromuscular blockade, the authors used simultaneously electromyography to monitor the laryngeal muscle and the diaphragmatic and adductor pollicis responses, while they used acceleromyography to monitor orbicularis oculi and corrugator supercilii responses. These two monitors are measuring two different physiological events. Electromyography measures the compound muscle action potential in response to nerve stimulation while acceleromyography measures the acceleration in movement resulting from muscle contraction and correlates this to force of contraction. While both monitors are acceptable monitors of neuromuscular blockade, they yield different results since each detects a different event. The results obtained from an electromyographic study cannot be used interchangeably or be compared to those obtained from an acceleromyographic one.

Nakata and colleagues studied the relationship between acceleromyography and electromyography in vecuronium-induced neuromuscular blockade.[2] They found that Tl/Tc values measured by acceleromyography were consistently lower than those measured by electromyography during recovery and that recovery was less rapid when measured by acceleromyography. They also found that the limits of agreement of Tl depression between acceleromyography and electromyography were too wide to use those measurement methods interchangeably, for when acceleromyographic Tl was 20%, electromyographic Tl varied between 11% and 82%.

Kitajima and colleagues found that electromyographic and acceleromyographic recorded duration of action of vecuronium block at the flexor hallucis brevis is different, even when recorded simultaneously in the same individual.[3] Ansermino and colleagues studied both acceleromyography and electromyography for the detection of residual neuromuscular blockade in children.[4] They found that the Tl response usually reappeared first in the EMG and was followed later by visual detection of Tl. The accelerographic response appeared only when two thumb twitches, on average, were observed visually.

It is, therefore, reasonable to conclude that although there may be a period of agreement between both types of monitoring when there is no twitch response, there is no agreement when measuring onset, duration of action or spontaneous recovery time. We think that the comparison that the authors made between these variables in five different muscles is invalid.

M. Elorbany
Y. Wafai
Department of Anesthesiology
Illinois Masonic Medical Center
Chicago, IL
USA

1 Hemmerling TM, Schmidt J, Hanusa C, Wolf T, Schmitt H. Simultaneous determination of neuromuscular block at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscles. *Br J Anaesth* 2000; **85**: 856–60
2 Nakata Y, Goto T, Saito H, Ichinose F, Uezono S, Suwa K, Morita S. Comparison of acceleromyography and electromyography in vecuronium-induced neuromuscular blockade with xenon or sevoflurane anesthesia. *J Clin Anesth* 1998; **10**: 200–3
3 Kitajima T, Ishii K, Kobayashi T, Ogata H. Differential effects of vecuronium on the thumb and big toe as measured by accelography and electromyography. *Anaesthesia* 1995; **50**: 76–8
4 Ansermino JM, Sanderson PM, Bevan DR. Acceleromyography improves detection of residual neuromuscular blockade in children. *Can J Anaesth* 1996; **43**: 589–94

Editor—Thank you for the opportunity to respond to the letter by Elorbany and Wafai. We agree that the comparison of neuromuscular blockade at different muscle sites using acceleromyography (AMG) and electromyography (EMG) has to be interpreted with caution. Theoretically, of all three monitoring techniques available (AMG, EMG and mechanomyography), EMG could most easily be used for all muscles. However, the separation of the response of the corrugator supercilii muscle from the response of the orbicularis oculi muscle using EMG is very difficult, if not impossible. EMG has so far only been used to monitor the response of the orbicularis oculi muscle via either surface[1] or subdermal needle electrodes.[2] These electrodes were positioned near the medial border and the central portion of the eyebrow. This position would rather reflect the response of the corrugator supercilii muscle and only partially, if at all, the response of the orbicularis oculi muscle.[3] Rimaniol and colleagues[4] therefore positioned the acceleromyographic probe on the upper eyelid to determine the response from the orbicularis oculi muscle. The corrugator supercilii is the focus of recent neuromuscular research to find a peripheral muscle which closely reflects the response of the larynx and diaphragm, and gives the clinician a useful estimation of laryngeal or diaphragmatic relaxation. AMG has been used to monitor neuromuscular blockade produced by succinylcholine and rocuronium at the corrugator supercilii muscle[5] and can be used distinctively at both the corrugator supercilii and orbicularis oculi muscle to monitor neuromuscular blockade; EMG cannot achieve this distinctive determination nor is it a monitoring tool used routinely in clinical practice. Our study design was the best compromise: it answers the question whether the acceleromyographic response of the orbicularis oculi or corrugator supercilii muscle using a commercially available and clinically established device (TOF-guard®) could be used to judge onset or offset of neuromuscular blockade at the larynx or diaphragm. Our clinically relevant result is: for mivacurium neither AMG of the corrugator supercilii nor AMG of the orbicularis oculi muscle reflect onset or offset of neuromuscular blockade at the larynx or diaphragm.

T.M. Hemmerling
Montreal
Canada

1 Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. *Anesthesiology* 1990; **73**: 870–5
2 Sayson SC, Mongan PD. Onset of action of mivacurium chloride. A comparison of neuromuscular blockade monitoring at the adductor pollicis and the orbicularis oculi. *Anesthesiology* 1994; **81**: 35–42
3 Goodmurphy CW, Ovalle WK. Morphological study of two human facial muscles: orbicularis oculi and corrugator supercilii. *Clin Anat* 1999; **12**: 1–11
4 Rimaniol JM, Dhonneur G, Sperry L, Duvaldestin P. A comparison of the neuromuscular blocking effects of atracurium, mivacurium, and vecuronium on the adductor pollicis and the orbicularis oculi muscle in humans. *Anesth Analg* 1996; **83**: 808–13
5 Plaud B, Donati F. The corrugator supercilii, not the orbicularis oculi reflects rocuronium neuromuscular blockade of the adductor laryngeal muscles. *Anesthesiology* 1999; **3**: A 1032

The use of salbutamol aerosol inhaler interferes with anaesthetic agent monitoring

Editor—A patient with a history of bronchial asthma underwent a gynaecological procedure under general anaesthesia. Anaesthesia was maintained at an end-tidal isoflurane concentration of 0.9% in a mixture of 56% nitrous oxide, measured by a Hewlett Packard M1026A anaesthetic-gas analyser. During the course of the operation, three puffs of an aerosol of salbutamol (Ventolin) at a concentration of 100 μg per puff were administered to the patient via a catheter mount adaptor connected to the tracheal tube and breathing circuit. It was noted a few seconds later that the anaesthetic-gas analyser now read ?agent 9.6%. The analyser was on auto mode at this time, and when isoflurane was specified on the analyser, it rapidly re-corrected the reading to 0.9%.

The Hewlett Packard M1026A anaesthetic gas analyser uses a technique called Non Dispersive Infra Red Gas Concentration Measurement. Salbutamol inhaler propellant contains trichlorofluoromethane (freon 11) and dichlorodifluoromethane (freon 12), and these substances absorb infrared light in the spectra used in the identification of potent inhalational agents.

It is probable that while on auto mode, the gas analyser covers a wider infrared wavelength range (10–14 μm) that includes that which is absorbed by the freon gas (about 12 μm), but when specifically instructed to detect isoflurane, the analyser uses a more specific wavelength of infrafred light, thus removing the contaminating effect of the freon gas.

We recommend that the anaesthetic agent used be specified on anaesthetic agent monitors to minimize erroneous readings, especially if freon-containing medications have to be introduced into the breathing circuit during the course of anaesthesia.

J. Tan
N. C. Hwang
Department of Anaesthesia and Surgical Intensive Care
Singapore General Hospital
Singapore

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Book Reviews

Transoesophageal Echocardiography in Anaesthesia. Jan Poelaert and Karl Skarvan (Editors). Published by BMJ Books, London. Pp. 687; indexed; illustrated. Price £95. ISBN 0-7279-1278-X.

This book comprises 16 chapters covering topics of interest to the echocardiographer anaesthetist, with contributions from some of the most prominent clinicians in this field. The range of subjects covered is extensive, from the principles of ultrasound to haemodynamic assessment and the transoesophageal echo (TOE) features of a wide range of cardiac pathology.

The emphasis in the text is on the intra-operative significance of echocardiographic findings. The editors have carefully included topics which may not find a place in standard echocardiography texts but are of particular interest to anaesthetists, such as the use of TOE to assist with cannula placement for minimally invasive cardiac surgery, and the assessment of air within the heart. This makes the book invaluable to anaesthetists, whose slant on the data provided by TOE often differs considerably from that of the cardiologists for whom most TOE texts are primarily intended.

The book is generously illustrated with black and white and colour images, which on the whole are of good quality and illustrative of the text.

The first chapter covers the physical principles of ultrasound. It is comprehensive, clear and easy to read (no mean feat for such a dry topic), with useful diagrams and echo images. The text presents the physics with accompanying explanations of how the principles described affect image acquisition and quality, which help to maintain the reader's interest.

The following chapter, written by the editors, deals with the manual manoeuvres required to acquire standard TOE images, as well as the practical aspects of cleaning and care of the TOE probe. The descriptions and diagrams are simple and clear.

The remaining chapters deal with the evaluation of myocardial performance, valve pathology, prosthetic function, intracardiac masses, the aorta, the assessment of ischaemia, training, and artefacts and pitfalls in TOE. The section covering congenital cardiac abnormalities, with information on both palliative and corrective surgery, admirably condenses a vast subject into a single chapter.

The authors have presented accounts of an almost uniformly high standard, with an emphasis on evidence-based discussion about the pros and cons of any particular method of assessment of a given parameter. The discussions are balanced and well referenced, with plenty of practical advice to aid intra-operative decision-making. I particularly enjoyed the chapter on left ventricular diastolic function, which elegantly clarifies a topic which could be considered something of a minefield.

Despite all this, the book is not perfect! I think that the section on mitral valve repair was disappointingly brief; the authors could have entered into much more detail about the surgical procedures available and the corresponding post-bypass echo appearances, particularly as TOE plays such a pivotal role in the intra-operative management of these patients. There is also no information on the use of TOE during transplantation surgery, a topic which could usefully have been included in a book such as this.

In addition to the occasional labelling error and the failure of standardization of some nomenclature (for example TOE *vs* TEE), there are many small grammatical and spelling errors that probably reflect the fact that English is not the native language of many of the authors. These errors could easily have been avoided by more careful proof reading. And while, for all I know, Michael Cahalan may be known as Dirty Harry to his friends. I suspect that the persistent misspelling of his name as Calahan throughout the book was not intended.

These errors are at times distracting, but on the whole do not detract greatly from the excellent quality of the book's content. This text would be an extremely valuable addition to the library of any echocardiographer anaesthetist, in particular those aiming for the American NBE examination in peri-operative TOE and, hopefully, the European equivalent in the future.

S.J. Wright
London

Local and Regional Anaesthesia. Per Rosenberg (Editor). published by BMJ Publishing Group, London. Pp. 164; indexed; illustrated.. Price £25. ISBN 0-727914804.

This compact volume is the latest in the *Fundamentals of Anaesthesia and Acute Medicine* series edited by Professors Jones, Aitkenhead and Foëx. This series is aimed at both established practitioners and trainees preparing for professional examinations, and seeks to bridge the gap between the large comprehensive text and the accelerating rate of biomedical advance. The intention is that each volume covers the fundamentals of the topic comprehensively, but emphasizes recent developments and controversies. My initial reaction to this was to wonder whether regional anaesthesia is a subject that would require such an approach, and my review was undertaken with that question very much in mind.

The first two chapters provide a comprehensive review of local anaesthetic drugs. In general, these would serve as a very good grounding for the trainee, but the opening of the first chapter is a little daunting, considering both the action of enantiomers at sodium channels and frequency-dependent block without any prior consideration of the anatomy or physiology of peripheral nerves. There is a first-rate consideration of individual drug properties and their systemic disposition, but not the emphasis that I might have expected on the newer agents, ropivacaine and levobupivacaine. Next, there is a consideration of some common local anaesthetic blocks by the editor. His introduction indicates that this is not a 'how to do it' book, but this chapter is, in essence, a somewhat superficial consideration of how to perform the common block techniques. It would serve as a useful overview for the beginner, but would not meet the needs of the FRCA candidate, nor would it be an adequate guide to clinical practice. Suprisingly, this is followed by a whole chapter devoted to intravenous regional anaesthesia, and one which could serve as a guide to clinical practice. It describes the benefits of prilocaine for this technique, and this emphasizes the concern that I feel at the recent withdrawal, on purely commercial grounds, of the appropriate preparation.

Chapter 5 is very much the 'jewel in the crown' of this volume. It is an excellent consideration (by Möllmann) of recent developments in the technology of needles, catheters and stimulators. For the regular practitioner of regional anaesthesia this chapter alone is worth the modest purchase price of the book. Almost as good is the following discussion (by Jakobsson) of the place of local techniques in ambulatory (a term I hate—what is wrong with day care?) surgery, considering the benefits, drawbacks and criteria for their use in this setting. However, it could have been improved by the presentation, in tabular form, of the discharge criteria for patients who have had blocks for day care surgery. The usefulness of such tabulated information is clear in the next chapter, in which Vercauteren considers regional

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techniques in obstetrics. your non-obstetric anaesthetist reviewer feels that all the current issues are covered well. The last two chapters, on controveries and complications respectively, both suffer from being short chapters with three authors each, presumably each individual contributing a section on a personal interest. The topics are current and appropriate, but the chapters are a little 'bitty'. At best, they would serve as sources of some relatively current information.

Overall this is something of a 'mixed bag', and I am not sure that it meets its aims, but it should certainly be on the shelf of anyone who has more than a passing interest in regional anaesthesia. The price is modest, the English is superb (particularly given that this is not the first language of any of the authors), and the illustrations are of a high standard, especially the photographs of needle tips in the chapter by Möllmann.

J.A.W. Wildsmith
Dundee

Obstetric Anesthesia Handbook, 3rd edn. Sanja Dattal. Published by Hanley and Belfus, Philadelphia. Pp. 400; indexed; illustrated. Price US$37. ISBN 1-56053-405-2.

This 400-paged, pocket-sized, single-author book is in its third edition. It is informative, integrated, indexed and referenced. Theoretical aspects are covered and there are practical tips throughout.

Overall it is a good book. It is up-to-date and comprehensive although perhaps a small section on fetal surgery might have been appropriate. Anaesthesia for *in vitro* fertilization is included. It is particularly helpful to have included a description of Scanlon's neurobehavioural score, something which is not in all such texts of this size. Minor criticisms include several typographical errors and imprecise use of English (e.g. page 187 'use of bicitra and metoclopramide 10 mg intravenously', implying that bicitra is also given intravenously). Furthermore, I think there has been some poor proof-checking as general anaesthesia for Caesarean section is quoted as having the disadvantage of taking a longer time and hence may not be ideal in acute fetal distress situations and may cause maternal discomfort!

It has to be admitted that the book is more directed at the American market having their spelling, terminology and drug names (e.g. Bicitra), and naturally reflecting obstetric anaesthetic practice in the USA. Althesin, for example, is recommended; I am surprised if it is still available.

I was pleased to see placenta accreta highlighted as important in placenta praevia. But I was surprised that haemorrhage is quoted as the overall number-one cause of maternal death. The implication was that this came from the Confidential Enquiries Report in the UK, where thromboembolism and hypertensive disorders of pregnancy are the leading causes of death.

Despite these criticisms, this is a useful book—British readers will need to compare it with UK texts of similar size and decide whether they prefer it or not. The wealth of information it contains is certainly impressive.

G.M. Cooper
Birmingham

Medical Biostatistics. Abhaya Indrayan and Sanjeev B. Sarmukaddam. Published by Marcel Dekker, Inc, New York. Pp. 645, indexed, illustrated. Price US$195. ISBN 08247-0426-6.

Statistics textbooks may be divided into three categories. The first are the large textbooks of statistical theory for those undertaking undergraduate and further studies in statistical method and practice. Secondly, there are books that are accessible, at least in part, to those with some knowledge of statistics and form useful reference texts. The third are textbooks from which the tyro may gain a glimpse of what statistics is all about and prepare for the single OSCE question in Primary FRCA. Within each group, the texts may be further classified under such headings as completeness and the clarity with which individual subjects are considered. This book is very much in the middle group, containing the usual statistical gamut with manageable mathematics. The authors intend the text to address the uncertainties encountered in medicine and to provide 'methods to measure the magnitude of these uncertainties and to minimise their impact on decisions'. It may be argued that this is what all such textbooks are for and the justification for publishing yet another book on the subject must be that the authors address topics not dealt with elsewhere or deal with the usual topics in a way that enables easier understanding. The 'primary target audience' is stated to be students, researchers and professionals of medicine and health but it is believed that practising biostatisticians might also be interested in the work; just about everybody then. The authors stress the 'heuristic' (pupils trained to find things out for themselves) explanations of statistical methods. This, I think, is to misunderstand the needs of medical people. They wish to be told what to do with all the collected data not where to look it up.

It is frequently difficult in statistics, as in many other parts of the medical curriculum, to understand topics from a single text. If struggling to comprehend, it is frequently helpful to approach the subject through other authors' eyes. In this sense therefore, it is useful for another comprehensive text to be launched. This is an extensive treatment of the subject running to upwards of six hundred pages. Those amateur statisticians grappling on a daily basis with, frequently, sketchy data from small projects will find it a useful work of reference. The examples given are relevant and the diagrams clear and appropriate. To those of a heuristic bent, the extensive reference sections are extremely useful; this aspect of textbooks is frequently inadequate. The book is well indexed.

It is very difficult to comment on the usefulness of what is, in effect, a work of reference until an adequate road test has been undertaken; first impressions are, however, favourable. The problems that the publishers of this book will encounter are those of a market saturated with textbooks of a similar nature. Whilst welcoming another view on the subject, I am not sure that the book passes the two tests that I set at the beginning of the review. It does not appear to contain anything new (I would have been surprised if it had), and the presentation of the subject is not measurably better (at the 95% level) than other competing text books. In the British market, it is in direct competition with, for example, Douglas Altman's book *Practical Statistics for Medical Research*. The small number of British anaesthetists who might be interested in a book of this relative complexity must examine the competitors and make their own decision.

D.A. Saunders
Southampton

International Anesthesiology Clinics. Current issues in anesthesiology, Volume 38, number 4, Autumn 2000. G. A. Maccioli (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 195, indexed, illustrated. Price US$208. ISBN 0020-5907.

This book is a slim volume in the continuing medical education style. It is aimed at a general readership, as the preface makes clear. It is a multi-author text, and indeed, many of the contributory chapters are multi-author, but the authors are experts in their fields. Multiple authorship can lead to a variable standard, but in this book it is generally high. The style is readable and lively. The book is very up-to-date, with many current and topical references. Although American in genesis, the editor and authors have managed to achieve what the series title suggests—they have produced a genuinely 'international' text which encompasses shades of opinion and practice of enviable breadth.

The chapters are organized in three logical groups. The first of these consists of four chapters representing advances in clinical practice in their respective areas. These are 'how you do it' master classes. I was a little disappointed in the chapter on the management of the septic patient in the operating room, which seemed rather general and more like a basic intensive care text than an advanced anaesthesia text. It is a difficult subject to cover, but the non-intensivist will glean a few gems from it. The next chapter covers the peri-operative management of selected endocrine disorders. Diabetes is a bit prolix, steadily improving through thyroid disease and phaeochromocytoma (magnesium not mentioned), and ending with a useful section on carcinoid tumours. The next chapter deals well with the management of intracranial hypertension, but does not mention 'medical' causes, such as hepatic failure, meningitis, or the role of lactate oxygen index in the assessment of critical ischaemia. The chapter on the airway in trauma is enjoyable, sensible and broad-minded. It includes use of such devices as the Laryngeal Mask Airway (LMA†) and the Combitube.

The next group of chapters deals with information-handling and technology. The chapter on automated information systems is thought-provoking, well-informed and a good read. The following chapter on the Internet is a little too basic for the computer-literate, but is up-to-date and includes some good web addresses. The third chapter, on theatre resource and utilization, is written from an American 'commercial' perspective, but should be read by all clinical directors and theatre managers as a salutary lesson: surgeons in the USA are no better at estimating the time of an operation than surgeons anywhere else!

The final group of three chapters deals with fluid management. The first of these, on fluid management in trauma, is good—and presents much stimulating evidence. The next, on transfusion practice in the operating room and intensive care unit, deals with transfusion triggers, transfusion practice, viral risk and so on. It is well referenced, clear, and very good. The final chapter is a *tour de force* by Kenneth Tuman, covering the use of the pulmonary artery (PA) catheter. He exposes many of the myths and misconceptions underlying the clinical misuse of this device. Anyone who uses PA catheters, or holds an opinion on them, would do well to read this salutary chapter. The book is slim, readable in a couple of evenings, enjoyable and informative. It is one of the better books of this type I have read. Sadly it is very expensive (US$208), so is more likely to be a departmental or library purchase than a personal one. But when you order a copy for your library, make sure people read it.

Mark Bellamy
Leeds

CD Review. Critical Incidents in Anaesthesia. Richard Griffiths and Jeremy Langton. Published by MMT Medical, Glaston Hall, Glaston, Oakham, Rutland LE15 9BZ, UK. ISBN 1.902940-07-5. Computer requirements: Pentium PC, 16x CD-ROM, 16Mb RAM, sound card and speakers, Windows 95 or later.

This is a CD-based computer learning package aimed at all grades of anaesthetists, from SHOs sitting the primary FRCA to the consultants who need to revise and update their core knowledge. The CD combines 'lecture' style teaching with self-assessment MCQs on a comprehensive range of critical incidents, and provides detailed, up-to-date information on causative factors, recognition and management. There is also some useful information on follow-up.

Loading the CD is a quick, easy process, which is 'read only', therefore avoiding installation to your hard drive. A splash screen is initially displayed which leads to the main menu, and some music that vaguely resembles the theme to BBC's 'Casualty' series. The main menu screen lists the 16 critical incidents covered, starting with cardiac arrhythmias during anaesthesia, then failed intubation, and finishing with accidental arterial drug injection and succinylcholine apnoea.

The choice of topics is comprehensive, and when compared to the list of critical incidents recommended for reporting in the Royal College of Anaesthetists logbook, little is left uncovered. However, there appears to be little discussion on critical incidents that are specific to subspecialties, for example, amniotic fluid embolism in obstetric anaesthesia. There also appears to be a lack of discussion on critical incidents caused by equipment faults or failures, something that occurs commonly, and can catch out even the most experienced anaesthetist.

Selecting one of these topics brings up the main interface. In essence, it is a latter-day tape-slide show. Forward and back buttons allow you to work through the material, and a brief narrative accompanies each screen of information provided by a male or female voice, which can be turned off if required. At the end of each topic a number of negatively marked multiple-choice questions with stems and five yes/no answers are available to test your understanding of the material. We found the questions were not very testing, and whether they are examination standard is unclear.

There is no doubt as to the quality of the information presented; it is all pertinent, concise and up-to-date. Core information is presented in a well-ordered and logical fashion, in what the sleeve notes describe as a 'short lecture' format.

The interface is well designed, passes the 'can you use it without a manual?' test, but (at least on our PC) makes limited use of the available screen area. What disappointed us was the way the information is presented. Each topic has between seven and 24 screens of information, and virtually all of them are lists or bullet-pointed text, which are static, and do not 'build' like animated electronic presentations.

The narrative is essentially the same text read aloud, albeit slightly paraphrased. We found reading text whilst listening to a slightly different narrative quite disconcerting at times. There are virtually no graphical screens; two algorithms are presented as flow charts and there are a few pictures of laryngoscopes and gum-elastic bougie. There are very few hyperlinks; a few references and pictures in one section make use of this technology but the majority of the sections are barren. The MCQ sections do make more use of the power of the computer, but though the computer artwork for the buttons, ticks and crosses is very elegant the underlying methods are fairly standard for computer-presented MCQs. There are few of the advanced features found in other MCQ based applications such as a 'Q-base', although perhaps there is no real indication for this technology here.

This CD undoubtedly contains all the important information about the topics that it covers. It will make a very useful addition to departmental teaching and we also think it will provide a useful resource for trainees who are concerned about their ability to recognize and deal with critical incidents. Whether publishing this information on a CD-ROM rather than paper makes this information more understandable or accessible is unclear.

David A.C. Wilkinson
J. Duncan Young
Oxford

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British Journal of Anaesthesia **86** (5): 742 (2001)

Erratum

Prospective evaluation of deep topical fornix nerve block versus *peribulbar nerve block in patients undergoing cataract surgery using phacoemulsification (BJA 2000; 85: 314–6)*

The units in column 1 line 16 were printed incorrectly. The line should have read as follows:

DTFNBA was performed using two sponges (2×3 mm) ...

The authors apologize for not noticing this error sooner, which could have avoided any confusion.

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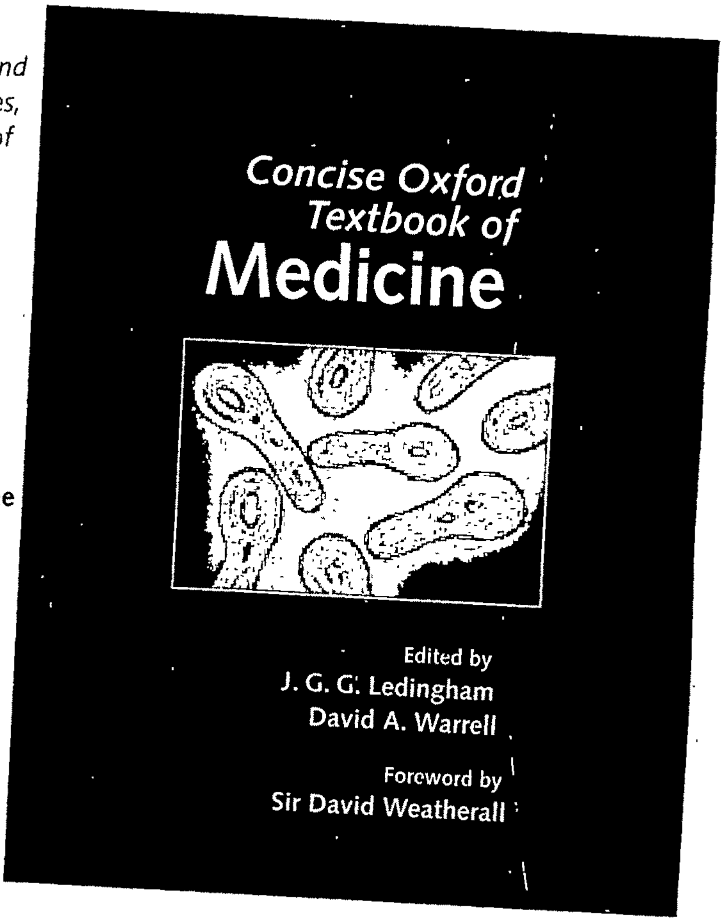

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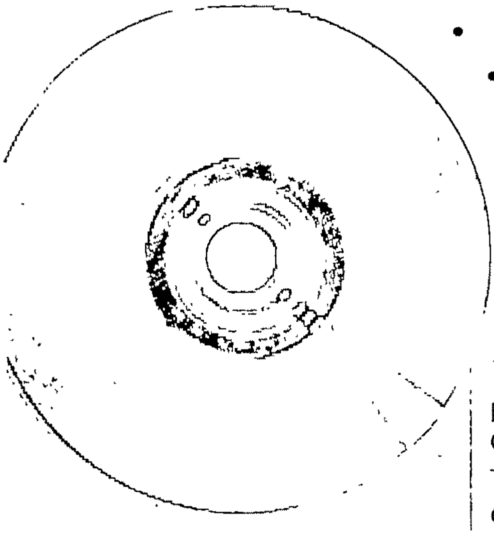

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From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

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Bradford Royal Infirmary, England, July 6, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

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Royal Lancaster Hotel, London, UK, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
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5th International Conference on Memory, Awareness and Consciousness: Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, NY, June 1–3, 2001

For further information, please contact: (for scientific enquiries) Ruth Reinsel, PhD, Department of Anesthesiology and Critical Care, Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6038; Fax: +1 212 772 8646; E-mail: mac@mskcc.org; website: www.maacc.org or (for other enquiries) Office of Continuing Medical Education, Box 31, Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA; Tel: +1 212 639 6754; Fax: +1 212 717 3140; E-mail: cmeinfo@mskcc.org; website: www. mskcc.org

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92; E-mail: SSAI.2001@rito.no
Web site: www.ssai2001.org

7th International Neuromuscular Meeting

Belfast, UK, June 21–24, 2001

For further information, please view the website http://www.nisca.org/nmb2001/ or contact Professor R. K. Mirakhur, Department of Anaesthetics and Intensive Care Medicine, The Queen's University of Belfast, Whitla medical Building, 97 Lisburn Road, Belfast BT9 7BL, Tel: 44 (0) 28 9033 5785; Fax: 44 (0) 28 9032 9605; E-mail: r.mirakbur@qub.ac.uk.

Abstracts are invited for presentation at the meeting. Please visit the website for instructions.

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: 0131 536 3652; Fax: 0131 536 3672; E-mail: anaes@ed.ac.uk

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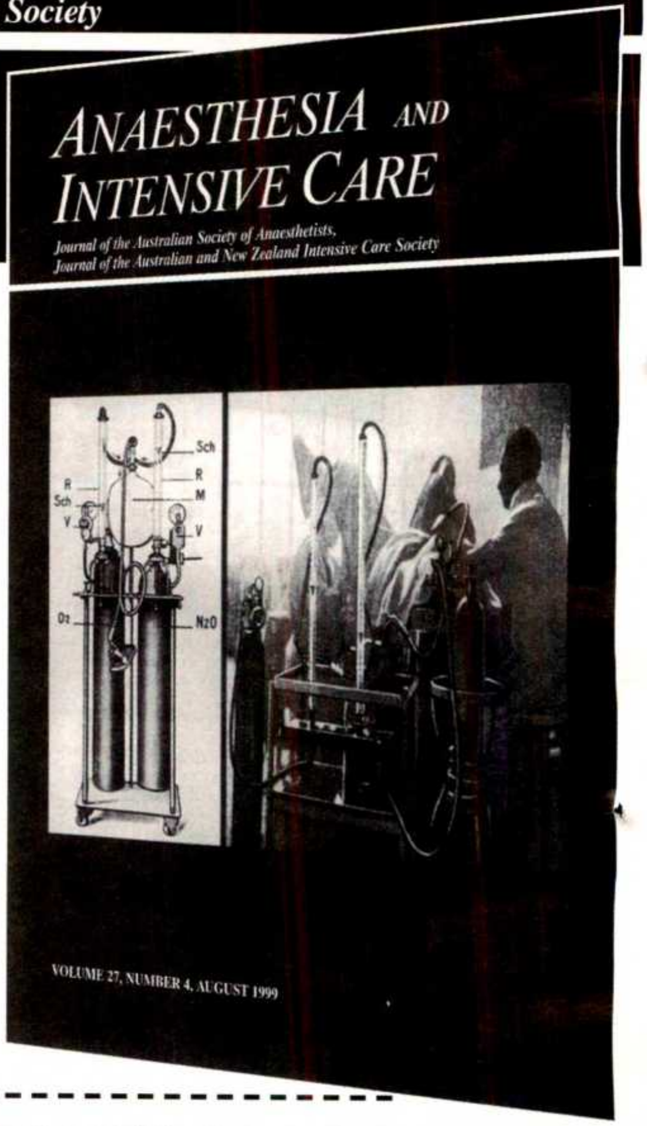
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Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

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ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

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ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

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For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

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Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

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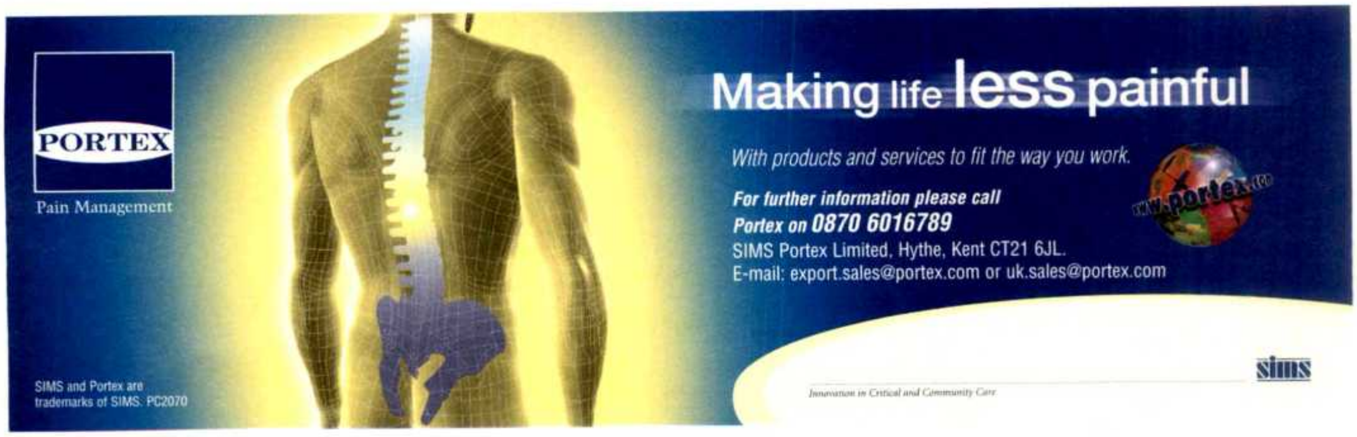
Bangalore, India, November 2–4, 2001



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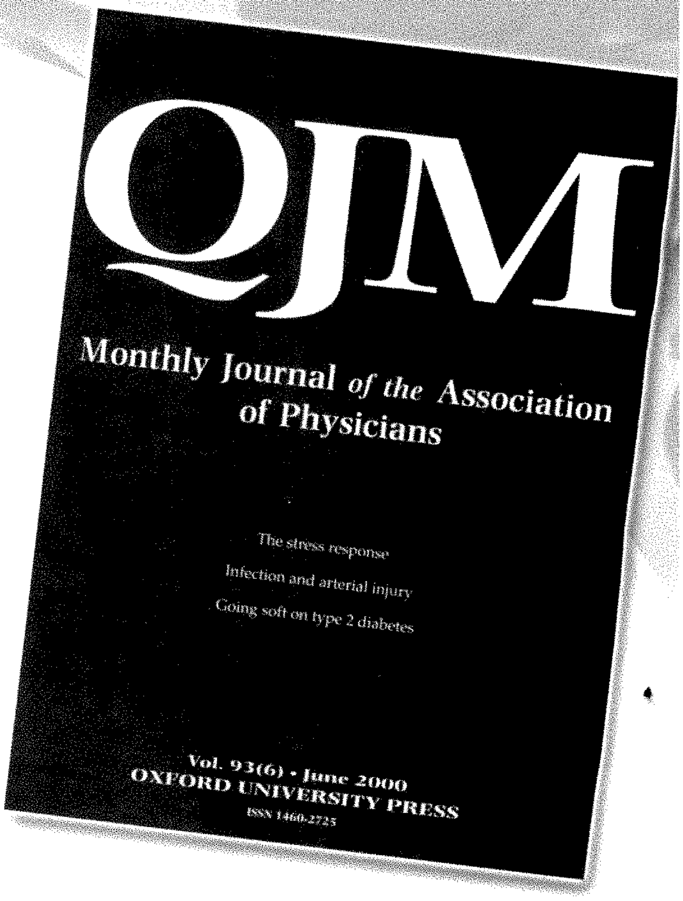

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For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

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Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

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First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

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Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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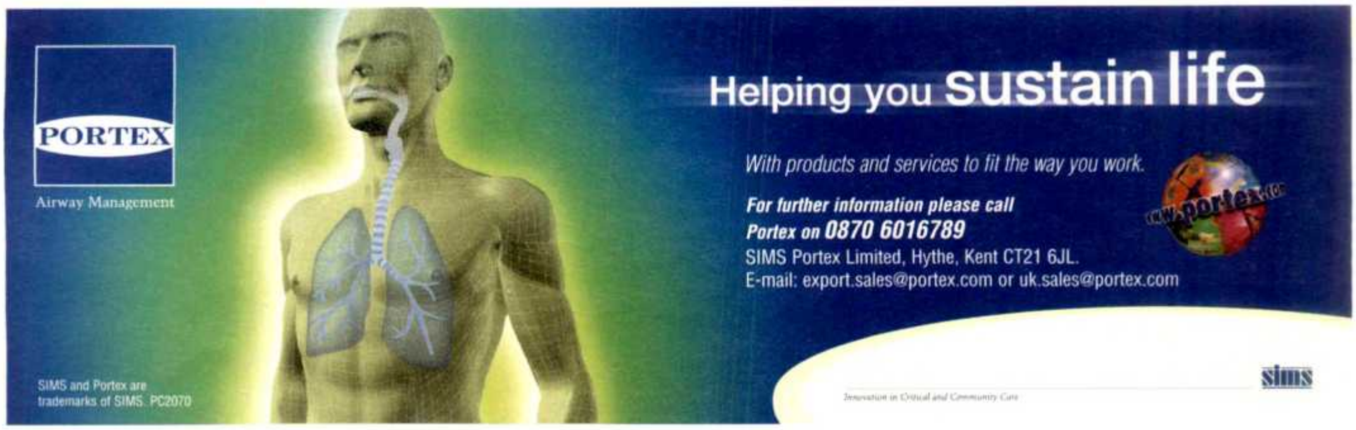

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8th International Congress of Cardiothoracic and Vascular Anesthesia
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Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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Abbreviated Prescribing Information
Moraxen® 35, 50, 75 and 100. Morphine® Sulphate 35, 50, 75 and 100mg. Please refer to SmPC before prescribing. **Indication:** For the short-term treatment of severe pain in advanced cancer when the oral route is no longer feasible for administering morphine. **Dosage and Administration:** Non dissolving suppository for rectal administration. Each Moraxen® unit should be inserted through the anus into the rectum. Up to two units may be inserted together, by applying a small amount of aqueous gel to each unit and the anal sphincter, to provide the following dosages 35, 50, 70, 75, 85, 100, 110, 125, 135, 150, 175 and 200mg. The dose conversion between 24-hour oral morphine and Moraxen® is 1:1. After approximately 24 hours Moraxen® should be expelled and replaced with another Moraxen® to continue pain management. If Moraxen® is lost prematurely due to defecation, a new Moraxen® should be inserted immediately. **Contra-indications:** Known sensitivity to morphine, morphine salts or hydrogel polymer components, respiratory depression, obstructive airways disease, acute hepatic disease, paralytic ileus, acute abdomen, diarrhoea, concurrent administration of monoamine oxidase inhibitors (MAOIs) or within two weeks of their discontinuation, head injuries, potential for raised intracranial pressure, painful conditions of the rectum or anus, neutropenia (<500 neutrophils/mm3) and in children aged 18 years or younger. In patients with rectal tumours producing excess mucus caution should be observed. **Warnings and Precautions:** Administer with caution in the elderly or debilitated, in severe renal or hepatic insufficiency, Addison's disease, myxoedema, hypothyroidism, prostatic tract, pancreatitis, inflammatory bowel disease, CNS depression, toxic psychosis, acute alcoholism, delirium tremens and convulsive disorders. Use in pregnancy only if the need for strong opioid analgesia justifies the potential risk to the foetus. **Undesirable effects:** Serious adverse reactions include respiratory depression and arrest, apnoea, circulatory depression, cardiac arrest, hypotension and/or shock. The most frequent less severe side effects include constipation, lightheadedness, dizziness, sedation, nausea, micturition disturbances, biliary colic, ureteric spasm, vomiting, sweating, dysphoria euphoria, dry mouth, headache, facial flushing, mood changes, palpitations, hallucinations, bronchospasm, colic, urticaria and pruritus. Rectal erythema and bleeding and anal irritation have been described in some patients. **Pack Quantities and Basic NHS Cost:** Blister packs of 7 units: £10.00 (35mg), £10.50 (50mg), £15.75 (75mg), £21.00 (100mg). **Legal Category:** POM, CD. **Product Licence Number:** PL 11937/0009 (35mg), PL 11937/0010 (50mg), PL 11937/0011 (75mg), PL11937/0007 (100mg). **Product Licence Holder:** CeNeS Drug Delivery Limited, Riverside Way, Riverside Business Park, Irvine KA11 5DJ, Scotland, United Kingdom. **Distributor (UK):** Schwarz Pharma Ltd., East Street, Chesham, Buckinghamshire, HP5 1DG, United Kingdom. Further information is available from: Schwarz Pharma Ltd., Schwarz House, East Street, Chesham, Buckinghamshire HP5 1DG (Telephone 01494 797 500). (1657). **Reference: 1.** Davis C. The role of a new 24-hour morphine hydrogel suppository (MHS) in palliative care. Eur J Palliat

SCHWARZ
PHARMA

VIOXX® ▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib. VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded. *Elderly:* Exercise care when increasing the dose from 12.5 mg to 25 mg. *Hepatic insufficiency:* In mild hepatic insufficiency, do not exceed 12.5 mg once-daily. *Children:* Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal

Third trimester of pregnancy and lactation. Inflammatory bowel
Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-e
significantly impaired renal function, uncompensated heart
or cirrhosis. Use caution when initiating treatment in patien
considerable dehydration. Rehydrate patients prior to s
therapy with rofecoxib. Consider the possibility of fluid retenti
exercise caution when rofecoxib is used in patients with pre-e
oedema, a history of heart failure, left ventricular dysfunc
hypertension. Maintain appropriate supervision when treati
elderly or patients with renal, hepatic or cardiac dysfunctio
rofecoxib. In clinical studies, some osteoarthritis (OA) patients
with rofecoxib developed perforations, ulcers or bleeds (
Patients with a prior history of a PUB and patients greater t
years of age appeared to be at a higher risk for a PUB. At daily
higher than 25 mg, the risks of gastro-intestinal symptoms,
or hypertension are increased. Elevations of ALT and/or A
times the upper limit of normal) have been reported in approxi
1% of patients in clinical trials with rofecoxib. Any patien
symptoms and/or signs suggesting liver dysfunction, or in wh
abnormal liver function test has occurred, should be evaluat
persistently abnormal liver function tests. If persistently abnorm
function tests (three times the upper limit of normal) are de
discontinue rofecoxib. Rofecoxib may mask fever. Use of rof

02-02 VOX 00 GB 65590 Ja

VIOXX®

Now with added VIGOR*

Landmark study supports superior GI safety profile compared with conventional NSAIDs

50% reduction in perforations, ulcers and bleeds (PUBs) compared with naproxen (95% CI 0.3-0.6; p=0.001)

*VIGOR – **V**IOXX **G**astro-intestinal **O**utcomes **R**esearch – a landmark study involving 8,076 rheumatoid arthritis patients monitored for GI events[1]. VIOXX is not licensed for rheumatoid arthritis. Patients were randomised to either VIOXX 50 mg once daily, or naproxen 500 mg twice daily for an average of nine months.

Rarely, patients may develop perforations, ulcers and bleeds with VIOXX, but the risk is lower in patients treated with VIOXX than in patients treated with conventional NSAIDs.

'VIOXX' IS LICENSED FOR OSTEOARTHRITIS ONLY, AT A DOSE OF 12.5 mg OR 25 mg ONCE DAILY

acodynamic): Warfarin: closely monitor the prothrombin time
ıen therapy with rofecoxib is initiated or changed in patients
ıg warfarin or similar agents, particularly in the first few days.
hibitors: administration of 25 mg daily of rofecoxib with
pril, 10 mg to 40 mg daily for four weeks to patients with
nsion was associated with a small attenuation of the
ertensive effect compared to the ACE inhibitor alone. This
be considered in patients taking rofecoxib concomitantly with
nhibitors. *Beta-blockers and diuretics:* concomitant use of
DS may reduce the antihypertensive efficacy of beta-blockers
retics and the other effects of diuretics. *Aspirin:* at steady state,
ib 50 mg once-daily had no effect on the anti-platelet activity
-dose (81 mg once-daily) aspirin. Avoid concomitant
stration of rofecoxib with higher doses of aspirin or other
DS. *Cyclosporin/tacrolimus:* monitor renal function when
ib and either cyclosporin or tacrolimus is used in combination.
tions (pharmacokinetic): Lithium: NSAIDS may increase
lithium concentrations. *Methotrexate:* consider adequate
ring for methotrexate-related toxicity when rofecoxib and
rexate are administered concomitantly. *CYP1A2 substrates:*
e care with concomitant administration of rofecoxib with drugs
ly metabolised by CYP1A2 (e.g. theophylline, amitriptyline,
and zileuton). *Midazolam:* a modest 30% reduction of the AUC
zolam was seen with rofecoxib 25 mg daily, most likely due
eased first pass metabolism through induction of intestinal
A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a
induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25-mg dose when rofecoxib is used with potent inducers of hepatic metabolism. Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *Pregnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus. *Lactation:* contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including
interstitial nephritis and nephrotic syndrome; hepatotoxicity includi
hepatic failure and jaundice.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspensi
12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers:

Tablet 12.5 mg: PL 0025/0383; Tablet 25 mg: PL 0025/03
Oral Suspension 12.5 mg/5 ml: PL 0025/0385; Oral Suspensi
25 mg/5 ml: PL 0025/0386.

Marketing Authorisation holder: Merck Sharp & Dohme Limi
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU. UK

POM **Date of review:** February 2001

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References:

1. Bombardier C, Laine L, Reicin A et al. Comparison of up
gastro-intestinal toxicity of rofecoxib and naproxen in patients w
rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528.

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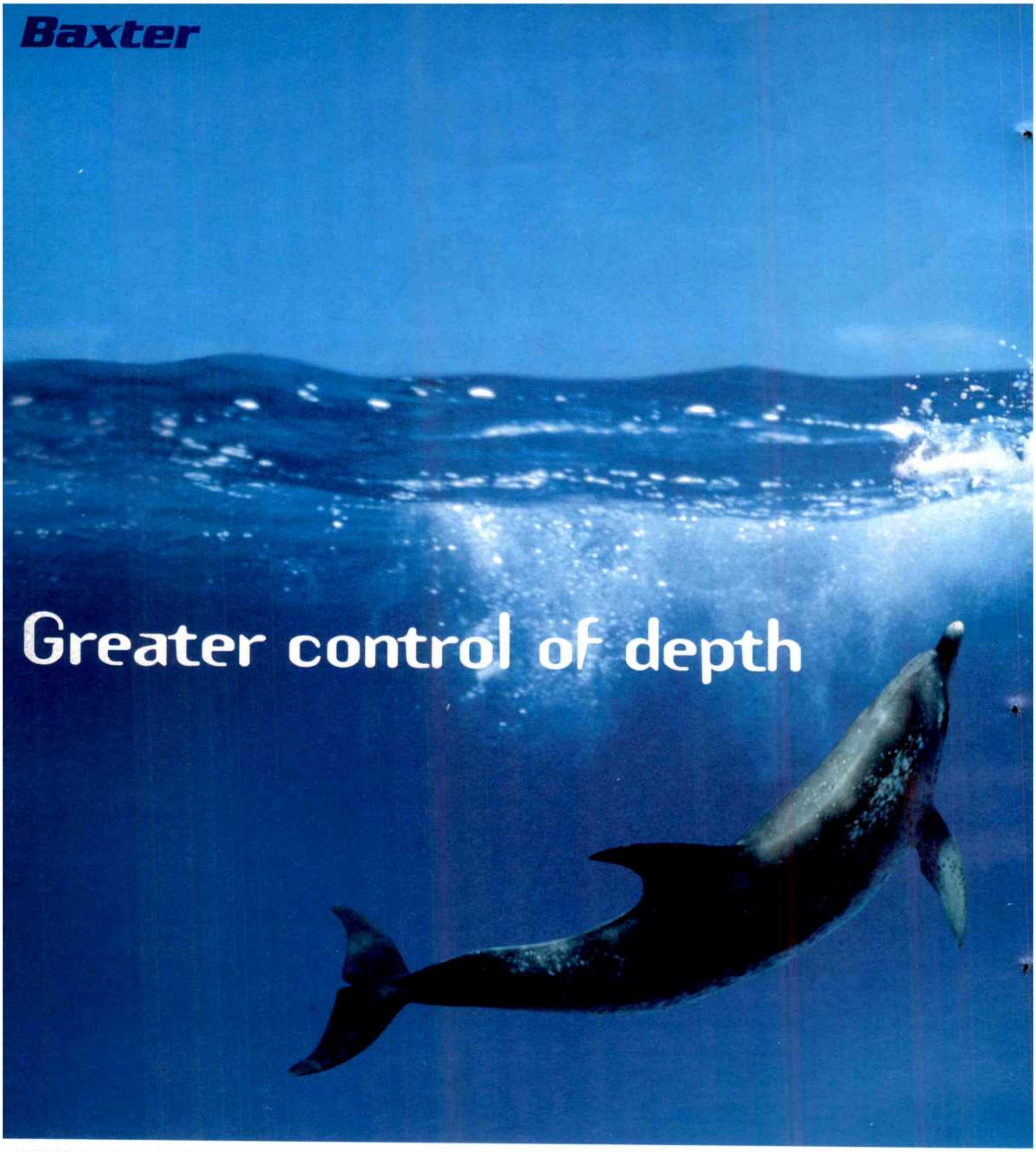

SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast

When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
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Precise control in
maintenance anaesthesia

SUP021/UK/0200

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK. (PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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*Haemoglobin levels >10 to ≤13 g/dL.

References:

1. Stowell CP, Chandler H, Jove M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

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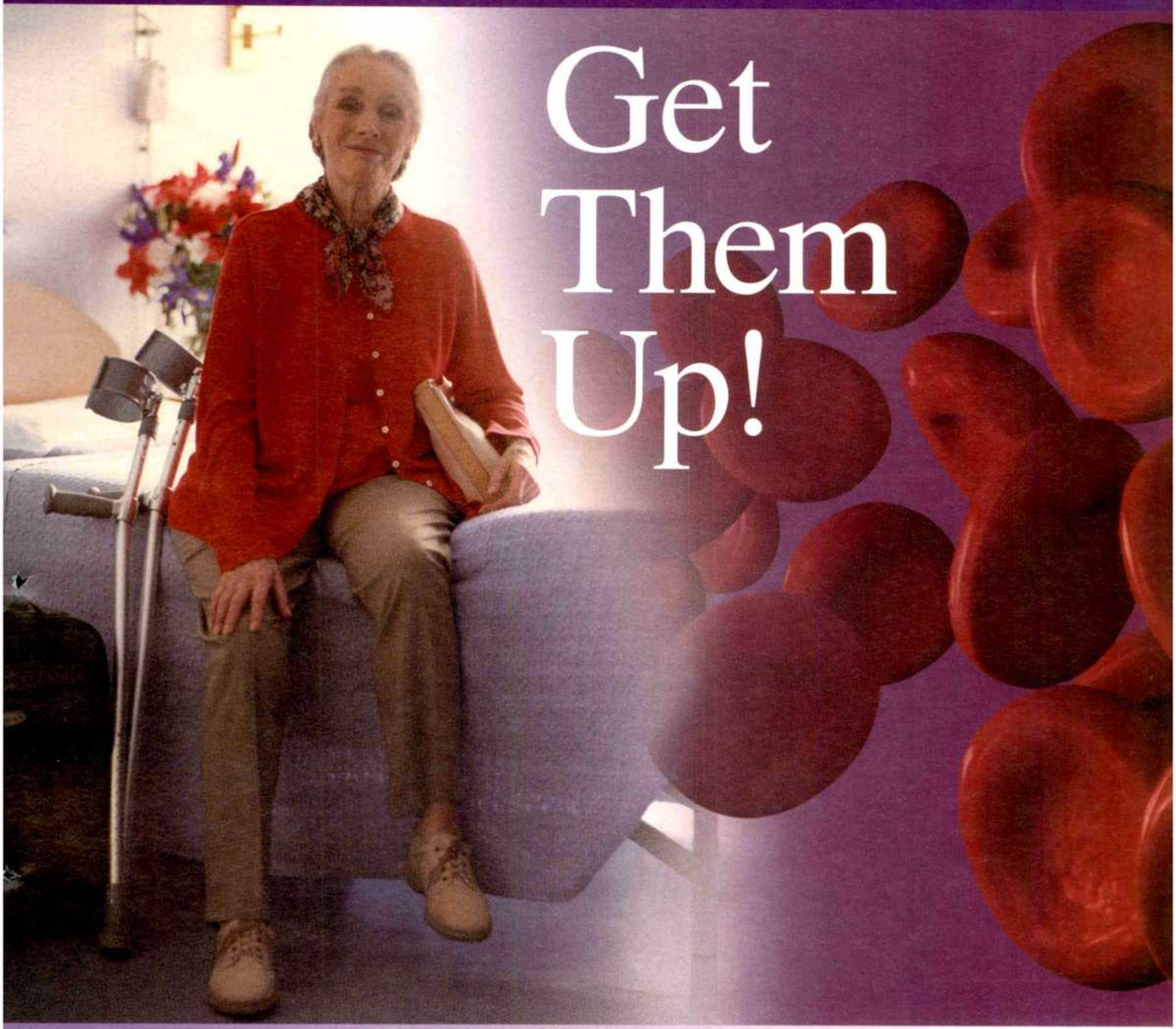

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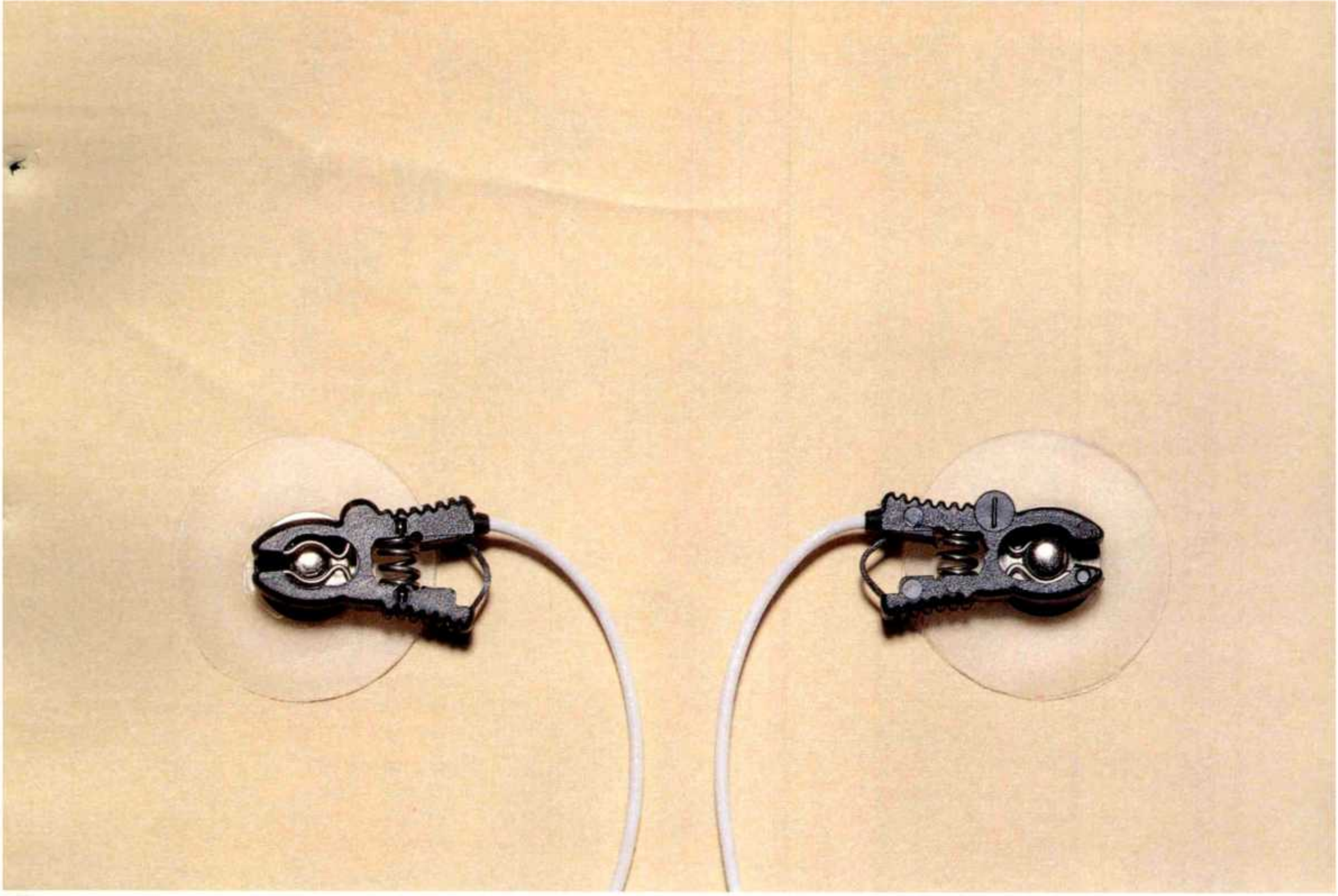

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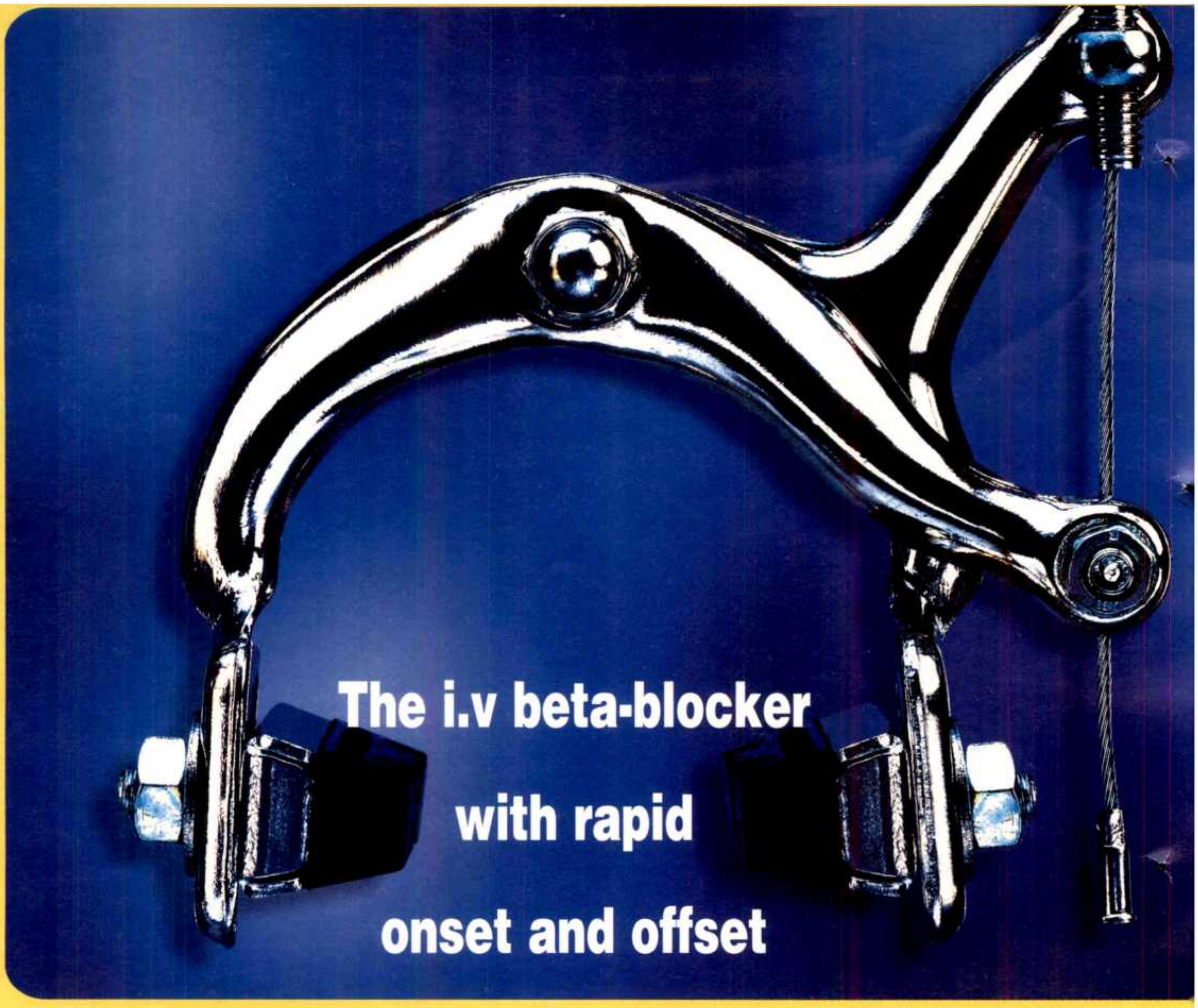

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Editorial I

Circulating volume and clinical assessment of the circulation

> *Experience teaches that to place reliance upon a single sign is precarious. Compare this sign and that, and confident recognition of the patient's state grows as these signs group themselves together to form a harmonious picture.*
>
> Sir Thomas Lewis[1]

One of the biggest critical care challenges is a septic patient with massive apparent fluid losses. The losses result from increased capillary permeability and third space sequestration, confounded by reduced vascular tone mediated through induced nitric oxide production, which might be associated with myocardial dysfunction.[2] These changes lead to a fall in cardiac output and profound hypotension, which result in poor organ perfusion, multiple organ failure and death. It would probably come as a surprise to most scientists, therefore, that, whereas clinicians have good techniques for measuring cardiac output, there are no easily undertaken bedside methods for measuring total circulating blood volume.

Circulating volume is a major determinant of cardiac output and it has been the response of the latter to fluid challenges that provides us with proxy assessments of circulating volume. Furthermore, it has been the achievement of good cardiac output rather than circulating volume which has consistently been related to better outcomes.[3–7]

Given the complex cause of changes in volume, blood pressure and cardiac output in sepsis, how should they be restored? Start by providing large quantities of intravenous fluid (6–10 litres of crystalloid or 2–4 litres of colloid) in order to obtain a blood pressure and a hyperdynamic state.[8] The type of fluid probably does not matter, but colloids tend to be less likely to cause pulmonary oedema at higher filling pressures.[9–11] Once volume resuscitation is 'complete', organ perfusion should be restored by increasing blood pressure to pre-morbid values with vasoconstrictors, because organ autoregulation is lost and perfusion becomes pressure dependent.[12] Norepinephrine on a full circulation seems to be in favour if dopamine is ineffective or has caused side-effects.[13] The resulting improved global circulatory state should provide a sustainable cardiac output for adequate organ function while specific therapies such as timely surgery and antibiotics prevent further insult.

What about the effect of all that fluid on systemic oedema and tissue oxygenation? Systemic oedema is an inevitable late development that follows fluid loading in patients with disturbed tissue permeability. It should not be a distraction to the prime target of achieving a full circulation. Furthermore, the effect of tissue oedema on tissue oxygenation is not necessarily deleterious.[14 15]

What about haemodynamic targets and monitoring? Use clinical end-points of perfusion in the first instance and insert an arterial line. If cardiac output is low, some measurement of pre-load and cardiac output is appropriate to guide inotrope requirements and avoid cardiac overload.

The foregoing guide sounds simple and should sound familiar. These are some of the latest evidence-based recommendations of the American College of Critical Care Medicine (ACCM) for the treatment of septic shock.[16] This excellent document exudes common sense but mostly surprises with its emphasis on clinical assessment in spite of the apparent advantages of technology that allows more and more accurate ways to measure pre-load and cardiac output.

The paper by Stephan and colleagues in this issue therefore comes as a timely reminder that clinical assessment of circulating volume as a first aim to adequate cardiac output in an individual still has a role.[17] But how can we seamlessly merge clinical art form and scientific measurement?

The importance of generous volume replenishment in septic shock was first seriously promoted by William Shoemaker and colleagues.[4 18–21] Shoemaker's approach at the time was brave considering that most intensivists were focused on drying patients to improve Pa_{O_2} in order to reduce FI_{O_2} to <0.6. Now most would agree that Shoemaker was right. However, when he suggested numerical haemodynamic targets that were subsequently applied prospectively in controlled studies the results were ambiguous.[5–7 22] Where patients did badly the proponents of goal-directed

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therapy suggested that the targets had been achieved with far too much use of inotropes. Unwittingly, the proponents had struck on the real problem, namely that the targets were population based rather than individually tailored, leading to some patients being driven with inotropes (possibly with insufficient volume) beyond their normal physiological limit. A recent study confirms the importance of physiological reserve for outcome.[23]

The effect of these studies was to tilt the emphasis towards volume resuscitation and to use inotropes to achieve pre-morbid blood pressure rather than specific oxygen transport targets. Then a spanner was thrown in the works when Connors and colleagues demonstrated that patient management guided by pulmonary artery flotation catheter, the current tool for guiding volume replacement, was associated with a poorer outcome.[24] At the time it was thought unlikely that this was due to complications of catheter placement,[25] which are relatively low,[26,27] but was more related to the way in which the information it provided was used.[28–31] So, paradoxically, after having been told that our clinical ability to assess haemodynamics is poor,[32,33] it seems that clinicians without the flotation catheter get better results.[24] Perhaps it is no longer time to ask what is the cardiac output but rather, is cardiac output effective?

How can we define an effective cardiac output (ECO)? The great Paul Wood, doyen of circulatory clinical assessment, firmly established the value of applying Ohm's law to bedside assessment and physiological measurement.[34] Blood pressure, which is directly related to the product of cardiac output and systemic vascular resistance, if compromised by fluid loss, stimulates sophisticated neuroendocrine compensatory activity. When acute this activity is revealed through clinical signs such as vasoconstriction, tachycardia and sodium retention (oliguria) in order to restore an effective cardiac output and, consequently, blood pressure. Chronic forms of compensated ineffective cardiac output are well recognized in conditions such as cirrhosis, nephrosis and chronic congestive cardiac failure where a sustained state of fluid retention and neuroendocrine activity coexists with a constant risk of organ failure at any further change in circulating volume status.[35]

An effective cardiac output, on the other hand, should have little need for compensatory mechanisms and individuals should be able to simultaneously have toes that are warm to the touch, and sustain their normal blood pressure preferably with a heart rate below 100 beats min^{-1}.[36,37] The absolute cardiac output is irrelevant in such circumstances. In the context of critical illness, a reasonable aim for an individual would be to achieve these same clinical end-points with some combination of fluids, vasoactive agent and inotrope. The advantage of clinical end-points for global perfusion is that they remain the same regardless of the phase of illness. The ACCM recommends additional end-points such as urine output and cerebral function; these could be included in a definition of ECO but may be unrelated to global perfusion due to previous established damage. Inevitably, clinical assessment is likely to vary with observer experience and therefore should be used with markers of improving cellular respiration. Furthermore, some patients, particularly those with poor cardiac function, may never reach these end-points; this is perhaps an omen of the likely outcome.

Do clinical end-points mean we can safely abandon all physiological measurement? Almost certainly not.[16] Measurements complement clinical assessment but do not replace it. They sometimes provide immediate diagnostic information, can provide confidence to undertake fluid challenges and help monitor trends towards the clinical target. Most significantly, measurement provides us with a language for information exchange. Whereas pulmonary artery catheter data may have been criticised for being poorly acquired, badly used or misleading,[38] alternative techniques have not yet been so tainted. Modern continuous methods such as oesophageal Doppler[39,40] and thermodilution-calibrated arterial pulse wave contour cardiac output[41] are widely used. These techniques might not confirm warm feet from their derived calculations but, when combined with clinical examination, might provide an appropriate numeric target for planning management during that specific phase of the illness.

Improved global perfusion should be associated with improving cellular metabolism. In spite of some well known problems such as lead time bias[42,43] and lack of specificity, indicators such as mixed venous oxygen saturation, acid–base balance and blood lactate are widely accepted as measures of anaerobic metabolism.[16] Progressive acidosis in spite of adequate global perfusion is suggestive of concealed regional ischaemia such as ischaemic hepatitis or bowel infarction. These conditions easily overwhelm buffering capacity and are rarely reversible by further increases in cardiac output. Perhaps the most successful tool for regional perfusion has been gastrointestinal tonometry,[44] which with hepatic venous flow and saturation changes[45–47] might find a niche for monitoring intestinal ischaemia particularly following vasoconstrictor therapy.

So where does the work of Stephan and colleagues[17] fit in? They have attempted to correlate clinical indicators—four markers of fluid overload and three suggestive of volume loss—with measurements of absolute circulating blood volume. They carefully selected stable critically ill patients to minimize confounding variables and defined hypovolaemia as a 10% deviation from expected calculated values for normal circulating blood volume. Their study concluded that a score based on clinical indicators of extracellular volume status reasonably predicted measured circulating hypovolaemia when that loss was approximately 1 litre. The study might be criticised for having some overlap in clinical indicators, using a nomogram as the control for circulating volume or possibly for assuming that a stable vascular compliance allows one to equate absolute circulating volume with effective circulating volume.

However, the message is clear: clinical assessment can be reasonably used to indicate volume status.

So might now be the time to apply a similar methodology to assessment of effective cardiac output? A daring start might be to break with tradition and assume this time that physical signs are the gold standard for an individual, and make the measurements in the presence and absence of signs. The volume and inotrope requirements to return to ECO might provide interesting and relevant information, particularly as we embark on outreach critical care.

M. Palazzo
Director of Critical Care
Charing Cross Hospital
London
UK

References

1 Lewis ST. *Disease of the Heart*, 3rd edn. London: Macmillan and Co., 1942

2 Parrillo JE, Parker MM, Natanson C *et al.* Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* 1990; **113**: 227–42

3 Shoemaker WC. Cardiorespiratory patterns of surviving and nonsurviving postoperative patients. *Surg Gynecol Obstet* 1972; **134**: 810–4

4 Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–86

5 Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; **102**: 216–20

6 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *J Am Med Assoc* 1993; **270**: 2699–707

7 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New Engl J Med* 1994; **330**: 1717–22

8 Rackow EC, Kaufman BS, Falk JL, Astiz ME, Weil MH. Hemodynamic response to fluid repletion in patients with septic shock: evidence for early depression of cardiac performance. *Circ Shock* 1987; **22**: 11–22

9 Virgilio RW, Rice CL, Smith DE *et al.* Crystalloid vs. colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979; **85**: 129–39

10 Rackow EC, Falk JL, Fein IA *et al.* Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983; **11**: 839–50

11 O'Brien R, Murdoch J, Kuehn R, Marshall JC. The effect of albumin or crystalloid resuscitation on bacterial translocation and endotoxin absorption following experimental burn injury. *J Surg Res* 1992; **52**: 161–6

12 Bersten AD, Holt AW. Vasoactive drugs and the importance of renal perfusion pressure. *New Horiz* 1995; **3**: 650–61

13 Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; **103**: 1826–31

14 Baum TD, Wang H, Rothschild HR, Gang DL, Fink MP. Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. *Circ Shock* 1990; **30**: 385–97

15 Rackow EC, Astiz ME, Schumer W, Weil MH. Lung and muscle water after crystalloid and colloid infusion in septic rats: effect on oxygen delivery and metabolism. *J Lab Clin Med* 1989; **113**: 184–9

16 Task Force of the American College of Critical Care Medicine SoCCM. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27**: 639–60

17 Stéphan F, Flahault A, Dieudonné N, Hollande J, Paillard F, Bonnet F. Clinical evaluation of circulating blood volume in critically ill patients. *Br J Anaesth* 2001; **86**: 754–62

18 Shoemaker WC, Printen KJ, Amato JJ, Monson DO, Carey JS, O'Connor K. Hemodynamic patterns after acute anesthetized and unanesthetized trauma. Evaluation of the sequence of changes in cardiac output and derived calculations. *Arch Surg* 1967; **95**: 492–9

19 Shoemaker WC. Priorities of resuscitation and subsequent therapy after trauma. *N Y State J Med* 1972; **72**: 1948–54

20 Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 1973; **106**: 630–6

21 Shoemaker WC, Kram HB, Appel PL. Therapy of shock based on pathophysiology, monitoring, and outcome prediction. *Crit Care Med* 1990; **18**: S19–25

22 Gattinoni L, Brazzi L, Pelosi P *et al.* A trial of goal-oriented hemodynamic therapy in critically ill patients. Sv_{O_2} Collaborative Group. *New Engl J Med* 1995; **333**: 1025–32

23 Velmahos GC, Demetriades D, Shoemaker WC *et al.* Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. *Ann Surg* 2000; **232**: 409–18

24 Connors AF, Speroff T, Dawson NV *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *J Am Med Assoc* 1996; **276**: 889–97

25 Soni N. Swan song for the Swan-Ganz catheter? *Br Med J* 1996; **313**: 763–4

26 Boyd KD, Thomas SJ, Gold J, Boyd AD. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. *Chest* 1983; **84**: 245–9

27 Smart FW, Husserl FE. Complications of flow-directed balloon-tipped catheters. *Chest* 1990; **97**: 227–8

28 Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *J Am Med Assoc* 1990; **264**: 2928–32

29 Nadeau S, Noble WH. Misinterpretation of pressure measurements from the pulmonary artery catheter. *Can Anaesth Soc J* 1986; **33**: 352–63

30 Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? *Crit Care Med* 1997; **25**: 213–20

31 Komadina KH, Schenk DA, LaVeau P, Duncan CA, Chambers SL. Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. *Chest* 1991; **100**: 1647–54

32 Rackow EC, Connors AF. Controversies in pulmonary medicine.

invasive measurements are required for assessing hemodynamic status in critically ill patients. *Am Rev Respir Dis* 1988; **138**: 1070–2

33 Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984; **12**: 549–53

34 Wood P. *Diseases of Heart and Circulation*, 2nd edn. London: Eyre and Spottiswoode, 1961

35 Rose B. *Clinical Physiology of Acid Base and Electrolyte Disorders*, 4th edn. New York: McGraw–Hill Inc., 1994

36 Joly HR, Weil MH. Temperature of the great toe as an indication of the severity of shock. *Circulation* 1969; **39**: 131–8

37 Palazzo M, Soni N. Critical-care studies: redefining the rules. *Lancet* 1998; **352**: 1306–7 [Erratum published in *Lancet* 1999; **353**: 848]

38 Gomez CM, Palazzo MG. Pulmonary artery catheterization in anaesthesia and intensive care. *Br J Anaesth* 1998; **81**: 945–56

39 Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. *Crit Care Med* 1991; **19**: 1132–7

40 Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Crit Care Med* 1989; **17**: 447–52

41 Buhre W, Weyland A, Kazmaier S *et al.* Comparison of cardiac output assessed by pulse-contour analysis and thermodilution in patients undergoing minimally invasive direct coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 1999; **13**: 437–40

42 Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983; **11**: 449–51

43 Falk JL, Rackow EC, Leavy J, Astiz ME, Weil MH. Delayed lactate clearance in patients surviving circulatory shock. *Acute Care* 1985; **11**: 212–5

44 Fiddian Green RG, Haglund U, Gutierrez G, Shoemaker WC. Goals for the resuscitation of shock. *Crit Care Med* 1993; **21** (Suppl): S25–31

45 Ruokonen E, Soini HO, Parviainen I, Kosonen P, Takala J. Venoarterial CO_2 gradient after cardiac surgery: relation to systemic and regional perfusion and oxygen transport. *Shock* 1997; **8**: 335–40

46 Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Crit Care Med* 1991; **19**: 1365–9

47 De Backer D, Creteur J, Noordally O, Smail N, Gulbis B, Vincent JL. Does hepato-splanchnic V_{O_2}/D_{O_2} dependency exist in critically ill septic patients? *Am J Respir Crit Care Med* 1998; **157**: 1219–25

Editorial II

A momentary pause...

In 1895, John Collins Warren, who previously had demonstrated ether anaesthesia, described sepsis as ‘a momentary pause in the act of death’. Since that time, little progress has been made to decrease the nearly 40% mortality associated with sepsis syndrome and septic shock. Sepsis syndrome is an increasingly prevalent clinical problem, which faces intensivists and anaesthetists. Mortality associated with this syndrome is high, thought to be 40–50%. There are approximately 1.5 million cases of sepsis each year in developed countries, with 750 000 cases per year in the USA alone.[1 2] The increasing incidence of this syndrome results from a number of factors, including increased use of immunosuppressive agents, a larger elderly population undergoing surgical procedures, and the development of antibiotic resistance. Although many sepsis patients undergo surgical procedures, little is known about optimal intraoperative management. In this issue, Allaouchiche and colleagues found that sevoflurane MAC was significantly decreased in sepsis patients.[3] This is an important contribution to the sparse anaesthesia literature that helps guide clinical management of septic patients when they come to the operating room. The findings of Allaouchiche and colleagues build on those of Gill and colleagues, who found a significant decrease in MAC for isoflurane in a rodent sepsis model.[4] It appears clear that sepsis syndrome results in decreased MAC in experimental models, and it is likely that this finding will hold true in humans. Aside from moderating doses of inhaled anaesthetics, what else can be done to optimize management of septic patients?

Pathophysiology of sepsis

Sepsis syndrome covers a spectrum of disease states, ranging from mild physiological disturbances, such as tachypnoea, fever and tachycardia, up to irreversible septic shock. The pathophysiology of sepsis is best understood as a systemic inflammatory response syndrome (SIRS) mediated by circulating cytokines that is triggered by bacterial or fungal organisms. Although originally described with Gram-negative organisms, with the inciting agent identified as lipopolysaccharide (LPS, or endotoxin), recent studies have identified that the incidence of SIRS associated with

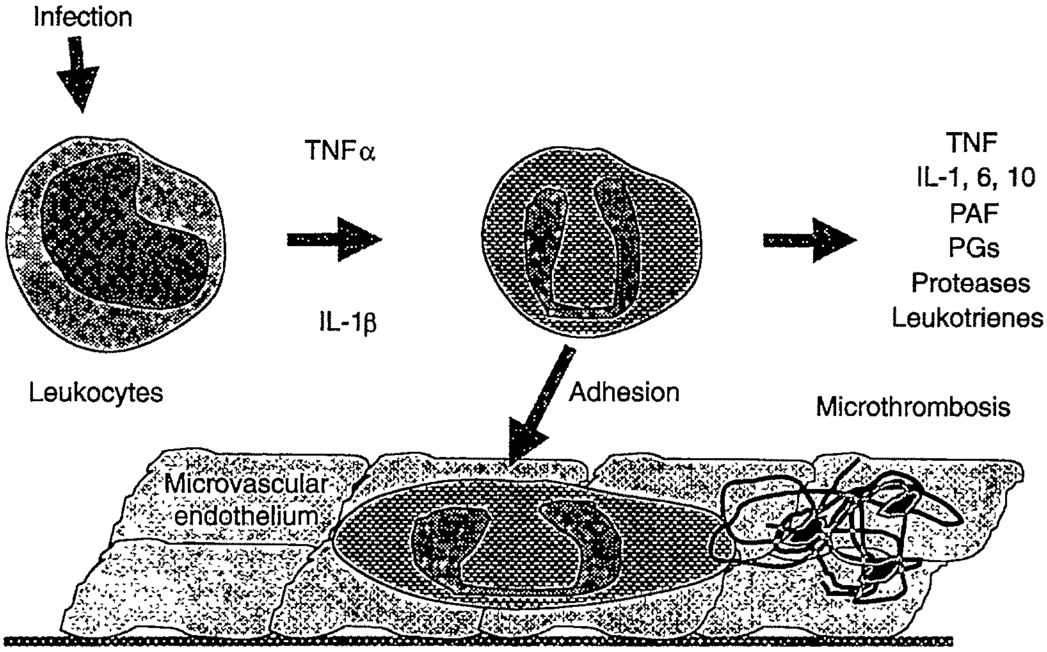

Fig 1 Early events leading to endothelial dysfunction in sepsis. An infectious agent triggers production of pro-inflammatory cytokines from leucocytes. These cytokines result in neutrophil–endothelial cell adhesion, activation of clotting and release of other inflammatory mediators. This endothelial injury eventually leads to multiple organ dysfunction syndrome. (Modified from Wheeler, *New Engl J Med*, 1994; **340**: 207–14.)

Gram-positive organisms and fungi is increasing in incidence.[5] Once an infectious agent triggers the inflammatory response, the syndrome that results is independent of the inciting organism. The physiological response is characterized by a state of overwhelming inflammation, which is soon followed by a state of relative immunosuppression.

Much has been made of the release of cytokines into the circulation with sepsis syndrome, and the majority of clinical trials have focused on neutralizing these proteins. The predominant cytokines found in the circulation early in sepsis syndrome are tumour necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β). TNF and IL-1 stimulate release of IL-6 and IL-8, both of which propagate the inflammatory cycle initiated by the infectious organism. Circulation of these cytokines results in widespread endothelial dysfunction, which underlies the multisystem organ failure (MSOF) that occurs, inevitably leading to death. Indeed, high levels of circulating cytokines correlate with mortality in sepsis syndrome.[6]

Clinical trials

In spite of promising laboratory studies, which showed that neutralization of cytokines significantly improves survival, clinical studies using this strategy have been uniformly unsuccessful.[7 8] The failure of these trials is probably a result of both the heterogeneous nature of sepsis syndrome and the naïve view that high levels of cytokines are uniformly harmful and should be blocked. The same molecules that are pro-inflammatory and cause tissue damage are essential components of host defence against infection. A more sophisticated approach to cytokine blockade might 'customize' therapy, with measurement of circulating cytokines and treatment based on their relative plasma concentrations and physiological effects. Although clinical trials of cytokine blockade continue, enthusiasm in the sepsis clinical trials community is waning.

Early investigations pursued the approach of increasing oxygen delivery in patients with septic shock. The foundation of this therapy was based on the work of Shoemaker and colleagues, who demonstrated that patients who survived septic shock tended to have higher oxygen delivery than those that died.[9] Since then, dozens of studies have examined the efficacy of increasing oxygen delivery in septic patients through the use of inotropes. The controversy continues; in 1993, Boyd and colleagues demonstrated decreased mortality in high-risk surgical patients who were treated with dopexamine to increase oxygen delivery.[10] Soon thereafter, Hayes and colleagues demonstrated increased mortality in patients treated with dobutamine to increase their oxygen delivery.[11] Given these conflicting findings, and a more recent, large, multicentre trial showing no efficacy, this approach cannot be recommended at this time.[12]

Sepsis and the coagulation system

Whereas most clinical trials in sepsis syndrome have concentrated on blocking the inflammatory response, recent focus has been on the coagulation pathway. Severe sepsis is associated with microvascular coagulopathy, which is evident by elevated fibrin-degradation products and thrombocytopenia. Severe microvascular dysfunction presents clinically as disseminated intravascular coagulation (DIC). Recent investigations have identified endothelial dysfunction with resultant coagulation abnormalities as a possible cause of the propagation of organ dysfunction in patients with sepsis. The hypothesis is that diffuse microthrombosis occurs in organ system beds, triggered by elevated levels of thrombin and tissue factor, resulting in a diffuse inflammatory response with subsequent MSOF. Figure 1 demonstrates this process.

There are a number of physiological mechanisms that help maintain homeostasis in the coagulation system. The primary anticoagulant molecules are activated protein C, antithrombin III and tissue factor pathway inhibitor (TFPI). These molecules act at the endothelial level to counteract activation of the coagulation pathway and prevent microvascular thrombosis. Acquired protein C deficiency is both prognostic of the development of sepsis syndrome and correlates with severity.[13] It is notable that protein C deficiency is present in the vast majority of patients with severe sepsis.[14] Protein C deficiency reflects severity of disease independent of the inciting pathogen (Gram-negative, Gram-positive, fungal or parasitic).[15] Whether endothelial dysfunction and MSOF may be preventable by repleting the anticoagulant molecules mentioned above is the subject of ongoing multicentre, international clinical trials.

Sepsis, the lung and mechanical ventilation

What else can be done to manage patients with sepsis when they come to the operating room? Since respiratory failure is the most common organ failure accompanying sepsis syndrome, much attention has been paid to preventing or limiting lung injury. The recognition that mechanical ventilation may injure the lungs has been recognized since the 1940s and the pioneering studies of Macklin and Macklin.[16] More recently, it has been recognized that overdistension of the lung can cause not only 'volutrauma', but also 'biotrauma', with release of cytokines such as TNF and IL-1 into the circulation.[17] A strategy known as lung-protective ventilation aims to avoid injury to the lung by limiting tidal volume and using increased levels of positive end-expiratory pressure (PEEP) to avoid cyclic alveolar collapse.[18] A recent multicentre trial conducted in the USA compared low tidal volume ventilation (6 ml kg^{-1}) with higher tidal volume (12 ml kg^{-1}).[19] This trial found a significant decrease in mortality (40% *vs* 31%) in patients ventilated with a 'low stretch' strategy. Lower tidal volumes are thought to decrease the propagation of lung injury by decreasing inflammatory activation. Not only might high tidal volumes increase inflammatory activation and circulating cytokines, but also in an animal model of *Pseudomonas aeruginosa* pneumonia, high tidal volume ventilation led to increased translocation of bacteria across the lung and into the circulation.[20]

What can we do to optimize the care of septic patients undergoing anaesthesia and surgery? Until more clinical trials are completed, there are no specific pharmacological interventions indicated. In patients with normal lungs, high tidal volume and low PEEP do not appear to be injurious.[21] However, low tidal volumes have been shown to decrease mortality in patients with acute lung injury and acute respiratory distress syndrome. Although most intensivists are familiar with protective ventilation strategies, anaesthetists also need to be aware of these data, and apply lung protective strategies to patients undergoing anaesthesia who are at risk for acute lung injury and sepsis.

M. A. Gropper
Anesthesia and Physiology
Critical Care Medicine and Cardiovascular Research Institute
San Francisco, CA
USA

References

1 Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *J Am Med Assoc* 1995; **273**: 117–23

2 Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Int Care Med* 2000; **26** (Suppl 1): S64–74

3 Allaouchiche B, Duflo F, Tournadre J-P, Debon R, Chassard D. Influence of sepsis on sevoflurane minimal alveolar concentration in a porcine model. *Br J Anaesth* 2001; **86**: 832–6

4 Gill R, Martin C, McKinnon T, Lam C, Cunningham D, Sibbald WJ. Sepsis reduces isoflurane MAC in a normotensive animal model of sepsis. *Can J Anaesth* 1995; **42**: 631–5

5 Rangel-Frausto MS. The epidemiology of bacterial sepsis. *Infect Dis Clin N Am* 1999; **13**: 299–312, vii

6 Dinarello CA. Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. *Chest* 1997; **112**: 321S–329S

7 Marshall JC. Clinical trials of mediator-directed therapy in sepsis: what have we learned? *Intensive Care Med* 2000; **26** (Suppl 1): S75–83

8 Kox WJ, Volk T, Kox SN, Volk HD. Immunomodulatory therapies in sepsis. *Intensive Care Med* 2000; **26** (Suppl 1): S124–8

9 Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 1973; **106**: 630–6

10 Boyd O, Grounds RM, Bennett ED. A randomized trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *J Am Med Assoc* 1993; **270**: 2699–707

11 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New Engl J Med* 1994; **330**: 1717–22

12 Gattinoni L, Brazzi L, Pelosi P, *et al.* A trial of goal-oriented hemodynamic therapy in critically ill patients. Sv_{O_2} Collaborative Group. *New Engl J Med* 1995; **333**: 1025–32

13 Boldt J, Papsdorf M, Rothe A, Kumle B, Piper S. Changes of the hemostatic network in critically ill patients—is there a difference

between sepsis, trauma, and neurosurgery patients? *Crit Care Med* 2000; **28**: 445–50

14 Fisher CJ, Yan SB. Protein C levels as a prognostic indicator of outcome in sepsis and related diseases. *Crit Care Med* 2000; **28**: S49–56

15 Mesters RM, Helterbrand J, Utterback BG, *et al.* Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. *Crit Care Med* 2000; **28**: 2209–16

16 Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. *Medicine* 1944; **23**: 281–352

17 Ranieri VM, Suter PM, Tortorella C, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *J Am Med Assoc* 1999; **282**: 54–61

18 Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Resp Crit Care Med* 1998; **157**: 294–323

19 Network ARDS. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New Engl J Med* 2000; **342**: 1301–8

20 Savel RH, Yao EC, Gropper MA. Protective effects of low tidal volume ventilation in a rabbit model of *Pseudomonas aeruginosa*-induced acute lung injury. *Crit Care Med* 2001; **29**: 392–8

21 Wrigge H, Zinserling J, Stuber F, *et al.* Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. *Anesthesiology* 2000; **93**: 1413–17

Note added in proof

Bernard *et al.* recently published an important multi-centre, randomized, placebo-controlled trial of the efficacy of protein C in severe spesis. They found that protein C decreased the relative risk of death by nearly 20% in patients with severe sepsis. There was a slightly increased risk of significant bleeding in the treatment group, and therefore caution should be exercised in patients at high risk for bleeding. This is the first large clinical trial demonstrating efficacy in severe sepsis syndrome, and protein C will likely become standard therapy for these patients.

Bernard GR, Vincent JL, Laterre PF, *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *New Engl J Med* 2001; **344**: 699–709

Editorial III

Is it safe to artificially ventilate a paralysed patient through the laryngeal mask? The jury is still out

The laryngeal mask airway (LMA[†]) was developed and introduced by Brain in 1983 with the intention of finding a compromise between a facemask and a tracheal tube.[1] Since then it has undergone various modifications including: the flexible tube has been reinforced; a bigger size has been introduced (no. 5); a change in shape has been made for the intubating laryngeal mask (ILMA);[2] and a different material has been used (silicon or polyvinyl chloride) for the disposable LMA.[3] The LMA is now used by some practitioners during percutaneous dilatational tracheostomy in the intensive care unit;[4] it has a firm place in the management of patients who are difficult to intubate;[5] and, by decreasing the incidence of dysphonia[6] and sore throat,[7 8] it is contributing to patient comfort, especially after day case surgery. In future, pharyngeal oximetry with the LMA may be a more accurate means of monitoring the Sa_{O_2} of unconscious patients than finger pulse oximetry.[9] It is undoubtedly one of the major developments in anaesthesia in the last 20 years.

It may seem inappropriate to secure the airway with an LMA if the patient has received a neuromuscular blocking drug and is to be artificially ventilated. The main concern would be pulmonary aspiration of regurgitated gastric contents. How often does this occur? In a meta-analysis in 1995, Brimacombe and Berry looked at 547 LMA publications which used various anaesthetic techniques for evidence of pulmonary aspiration and found that the incidence was only two in 10 000 (0.02%).[10] Most cases had predisposing risk factors for pulmonary aspiration; no deaths occurred.

It may be thought that the LMA is used predominantly in spontaneously breathing patients but a survey of its usage in the UK in 1996 revealed that 5236 of 11 910 patients (44%)

[†] LMA® is the property of Intavent Limited.

underwent positive pressure ventilation through the LMA.[11] It is not clear how many of these patients had received a neuromuscular blocking drug. This survey showed a very low rate of critical incidents associated with LMA use in conventional (0.16%) and non-conventional practice (0.14%). Non-conventional use of the LMA at that time included for operations such as abdominal hysterectomy (404 patients), gynaecological laparotomy (240 patients), laparoscopic cholecystectomy (65 patients), colectomy (14 patients) and even elective abdominal aortic aneurysm (seven patients). Ventilation was controlled in 77.4% of patients undergoing laparoscopy and 97% of patients undergoing laparotomy. Three cases of failed intubation were managed with a laryngeal mask. There were 44 (0.37%) critical incidents of which 18 were related to the airway. Regurgitation occurred in four patients (0.03%) and vomiting in two (0.017%), but proven aspiration of gastric contents occurred in only one patient (0.009%). Laryngospasm or bronchospasm (which could have been due to aspiration) occurred in 11 patients (0.095%). A slightly higher percentage of critical airway incidents occurred in patients undergoing positive pressure ventilation compared with spontaneous ventilation (0.21% vs 0.11%) through the LMA, but the difference did not reach statistical significance. How often would such adverse events have occurred during artificial ventilation using a cuffed tracheal tube in a paralysed patient? Few large prospective randomized comparisons exist.[7] Undoubtedly, there is a need for further study in this area.

Innovation in anaesthesia is judged in the light of risk–benefit analysis. The risk of an adverse event associated with a new anaesthetic technique should be less than that in older, well accepted techniques and it should improve outcome. Is there any indication for positive pressure ventilation through the LMA or is it disadvantageous? Is it affected by the use of neuromuscular blocking drugs in combination with positive pressure ventilation?

Advantages of the LMA

In 1995, Brimacombe summarized the advantages and disadvantages of the LMA compared with tracheal intubation as derived from yet another meta-analysis.[12] The advantages included: haemodynamic stability at induction compared with intubation, and during emergence compared with extubation; minimal increase in intraocular pressure after insertion; reduced anaesthetic requirements for airway tolerance; lower frequency of coughing during emergence; improved oxygen saturation during emergence; and a lower incidence of sore throat in adults. Ferrari and Goudsouzian have demonstrated that the use of a LMA in ex-premature infants and children with bronchopulmonary dysplasia undergoing second-stage vitrectomy as a daycase procedure produced less desaturation, coughing, wheezing and hoarseness than a tracheal tube.[13] The children in the LMA group were discharged home earlier.

Keller and Brimacombe demonstrated that the LMA impairs mucociliary clearance, as measured by mucus transport velocity, less than a tracheal tube.[14] The authors postulated that this may have implications for reducing the risk of retention of secretions, atelectasis and pulmonary infection. A cost analysis study proved that the LMA was the most cost-efficient airway choice if it is reused 40 times, and each anaesthetic lasted for >40 min.[15]

Thus there appear to be advantages in using an LMA instead of a tracheal tube, mainly in reducing the minor morbidity associated with anaesthesia. Are there disadvantages?

Disadvantages

The main complications of using a LMA relate to the airway seal pressure of its cuff. The LMA cuff seal pressure is the inflation pressure above which gas can escape around the cuff. This is lower than with a tracheal tube, so there is a greater risk of gastric insufflation, gastro-oesophageal reflux and aspiration of regurgitated gastric contents when using an LMA.[12]

Gastric insufflation

The lower seal pressure of an LMA might cause difficulties in patients unexpectedly requiring high airway inflation pressures for adequate oxygenation; this is pertinent when pressures reach 19–33 cm H_2O.[16] Devitt and colleagues studied gastro-oesophageal insufflation in 48 patients who received neuromuscular blocking drugs and controlled ventilation through the LMA.[17] Gastro-oesophageal insufflation and gas leak were assessed by a single investigator, blinded to the ventilating pressures, by placing a stethoscope over the stomach and neck respectively during artificial ventilation. Gastro-oesophageal insufflation occurred in only 2.1% of patients at inflation pressures of 15 cm H_2O but increased to 35.4% at 30 cm H_2O.

A lower frequency of gastro-oesophageal insufflation was found by the same group of workers in a study of 60 artificially ventilated patients using the LMA or a facemask; in the LMA group, it occurred in one patient at an inflation pressure of 20 cm H_2O and in three patients at 30 cm H_2O.[18] Keller and colleagues looked at 164 unparalysed patients during either spontaneous or positive pressure ventilation who underwent peripheral musculoskeletal surgery.[19] Peak airway pressure was limited to 15 cm H_2O. No gastric insufflation was detected using the same clinical method as Devitt and colleagues, i.e. epigastric auscultation. As there are limitations to this technique, Weiler and colleagues used an epigastric microphone, which could detect as little as 2 ml of air entering the stomach.[16] In this study, eight of 30 patients (27%) experienced gastric insufflation at inspiratory pressures between 19 and 33 cm H_2O.

A size 5 LMA can provide a better seal for positive pressure ventilation and reduce the incidence of air leak.[20 21]

Brimacombe investigated the safety and efficacy of a size 5 LMA in 179 patients undergoing positive pressure ventilation using a neuromuscular blocking drug.[20] He demonstrated that none of the patients had gastric insufflation at tidal volumes of 8 ml kg^{-1} and an oropharyngeal leak only occurred in 0.7% of patients. He suggested that positive pressure ventilation with the size 5 LMA is safe and effective. A low failure rate (3%) was seen even in patients who were moderately obese (body mass index >30 kg m^{-2}). There was no correlation between the incidence of complications, leak pressure and body mass index.

Maltby and colleagues recently investigated the incidence of gastric distension during laparoscopic cholecystectomy in 101 patients paralysed and ventilated through an LMA or a tracheal tube.[22] The incidence and degree of gastric distension was similar in both groups. However, importantly, these investigators noted that their randomized controlled study was too small to determine the risk of aspiration pneumonitis when using an LMA.

Regurgitation into oesophagus

Regurgitation and aspiration with the LMA are more commonly associated with periods of light general anaesthesia,[10] or placing the patient in the Trendelenburg or lithotomy position.[23] El Mikatti and colleagues used methylene blue to detect regurgitation in patients receiving an LMA.[24] They demonstrated that one of 30 patients in the Trendelenburg or lithotomy position had regurgitation, but none experienced it in the supine position. Valentine and colleagues investigated the incidence of reflux during positive pressure ventilation through the LMA or a tracheal tube in 20 paralysed patients undergoing cataract surgery.[25] All patients were ventilated to normocapnia and tidal volumes adjusted to maintain a peak inflation pressure of 16 cm H_2O. Four out of 10 patients in the LMA group and one out of 10 patients in the tracheal tube group had mid-oesophageal reflux during anaesthesia. The incidence of reflux after antagonism of residual neuromuscular block was even higher in the LMA group but none of the patients had any clinical evidence of adverse sequelae. Reflux was measured with a pH electrode placed in the mid-oesophagus.

Brain and colleagues have suggested that the LMA seal interferes with upper oesophageal sphincter tone, and this tone may also be affected by insertion of a pH electrode into the oesophagus or by the return of muscle power to the larynx and pharynx during antagonism of residual neuromuscular block.[26] Agrò and colleagues studied oesophageal pH values associated with the LMA and positive pressure ventilation in 82 paralysed, supine orthopaedic patients.[27] Neuromuscular block was allowed to wear off spontaneously. There were no reflux events into the oesophagus (pH <4.9) during any phase of anaesthesia. Agrò and colleagues stated with 95% confidence that the probability of gastro-oesophageal reflux is less than 4.6% when the LMA is inserted by skilled users. Bapat and Verghese came to a similar conclusion in a study of the incidence of regurgitation during gynaecological laparoscopies, when the patients were given a small dose of atracurium and artificially ventilated through the LMA; they suggested that the probability of regurgitation is <4.1%.[28] Owens and colleagues compared the incidence of gastro-oesophageal reflux in 55 patients breathing spontaneously through the LMA or facemask.[29] They observed reflux episodes in the LMA group in 53.6% of patients into the mid-oesophagus and 21.4% into the upper oesophagus; there were multiple reflux episodes in 28.6%. In each instance, the incidence of reflux was greater in the LMA group than in the facemask group, but there was no clinical evidence of pulmonary aspiration of gastric contents.

Aspiration of gastric contents

Regurgitation and aspiration occasionally occur in all types of anaesthetic practice. Warner and colleagues investigated the Mayo Hospital database of 215 488 general anaesthetics given between 1985 and 1991 (not involving the use of the LMA) for clinically significant events of pulmonary aspiration during the perioperative period.[30] Fifteen aspiration episodes occurred during 13 427 anaesthetics (0.11%) in patients undergoing emergency surgery and 52 occurred in 202 061 anaesthetics (0.025%) in patients undergoing elective surgery. The complications occurred either during artificial ventilation with the facemask, preceding tracheal intubation, or after extubation. *None* occurred when the trachea was intubated. Of the 66 patients who aspirated and survived surgery, 13 required ventilatory support postoperatively, three of whom died.

How often do such events occur with the LMA? Such a large, retrospective study including the LMA does not yet exist. Although not as useful as a prospective randomized comparison with tracheal intubation, it would provide interesting, evidence-based information.

Critical incidents from LMA usage

In 1990, Griffin and Hatcher reported the case of a 26-year-old woman weighing 60 kg with no previous medical history who underwent elective cholecystectomy.[31] After induction of anaesthesia, neuromuscular blockade was established with vecuronium 6 mg and a size 3 LMA inserted. Anaesthesia was maintained with enflurane in nitrous oxide and oxygen. The patient was ventilated with a tidal volume of 430 ml and a peak inspiratory pressure of no more than 1.5 kPa (15 cm H_2O). The duration of surgery was 1.5 h. Spontaneous ventilation was allowed to return without antagonism of residual neuromuscular block, which may be a significant factor. At the end of surgery, the patient was placed in the left lateral position to carry out intercostal nerve blocks. The LMA was removed after bile-stained fluid was noted within the LMA tube lumen. A chest X-ray showed left-sided aspiration pneumonia. The patient was closely monitored on the intensive care unit but did not require artificial ventilation. She made a good recovery.

In 1992, Nanji and Maltby described a critical incident in a 74-year-old man who underwent an arthroplasty for fracture of the femoral neck.[32] He had Alzheimer's disease and a history of peptic ulcer for which he had required oesophageal dilatation, but he had not had any symptoms of reflux, as far as could be ascertained, for more than 20 years. A size 4 LMA was inserted after induction of anaesthesia with thiopental and fentanyl, and anaesthesia was maintained with isoflurane, with the patient breathing spontaneously. The patient was placed in the right lateral position for surgery, which continued uneventfully until the femoral head was pulled from the acetabulum. At that time, the patient took several deep breaths and the Sa_{O_2} decreased from 98% to 85%. Gastric content was observed at the corner of the patient's mouth. After immediate tracheal intubation, auscultation did not reveal any wheezing or decreased air entry, although gastric contents were observed in the anaesthetic circuit. The patient vomited again around the tracheal tube at the end of surgery. Bronchoscopy did not show any particulate matter. Nevertheless, the patient required artificial ventilation for 4 days after surgery with an Fi_{O_2} of 1.0 and positive end-expiratory pressure. He subsequently recovered and was discharged to the ward.

In 1996, Ismail-Zade reported a case of regurgitation and aspiration of gastric contents in an asthmatic child anaesthetized for elective orthopaedic surgery using an LMA.[33] Ten minutes after induction, brown fluid was noted in the LMA tube and the patient's arterial oxygen saturation decreased from 96% to 86%. Tracheal intubation was effected and brown fluid was also noted in the tracheal aspirate. Bronchospasm developed which worsened after surgery. Chest X-ray revealed patchy consolidation of the right upper lobe. After antibiotic and bronchodilator therapy, the patient made a good recovery.

Would these patients have regurgitated and inhaled gastric contents if a tracheal tube had been used? Is the number of such reports small because they are no longer considered new (and therefore interesting)? Or is the incidence of such critical incidents truly low? Representatives of the Medical Defence Union could not confirm any incidents, but the NHS Litigation Authority have received a complaint arising from a critical incident associated with the ILMA (personal communication, J. Mead).

A concluding paradox

Thus, evidence from studies undertaken in relatively small numbers of patients (mainly by experts in LMA insertion), and the small number of critical incidents reported, suggest it is safe to ventilate a patient artificially through an LMA. But consider further the findings of Verghese and Brimacombe[11] in relation to anaesthetic practice in the UK. The incidence of proven aspiration using the LMA in Verghese and Brimacombe's retrospective study was 0.009%. If about four million anaesthetics are given in the UK each year, this would amount to about 360 such incidents. Warner and colleagues[30] reported that three of the 66 patients who aspirated and survived surgery in the Mayo clinic study died. Thus one might expect about 16 deaths each year in the UK from aspiration of gastric contents when using the LMA (3×360/66). This would equate with one death in each region of the UK each year. Such considerations are reminiscent of determining the risk of spinal haematoma after epidural anaesthesia in patients on heparin, or hepatitis after exposure to halothane. They are rare. But we suggest that the time has not yet come to pass when we can appreciate fully the risks of artificially ventilating a patient through an LMA.

G. Sidaras and J. M. Hunter
University Department of Anaesthesia,
University Clinical Department,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA,
UK

References

1 Brain AIJ. The laryngeal mask—a new concept in airway management. *Br J Anaesth* 1983; **55**: 801–5

2 Brain AIJ, Verghese C, Addy EV, Kapila A. The intubating laryngeal mask. I: Development of a new device for intubation of the trachea. *Br J Anaesth* 1997; **79**: 699–703

3 Brimacombe J, Keller C, Morris R, Mecklem D. A comparison of the disposable versus the reusable laryngeal mask airway in paralyzed adult patients. *Anesth Analg* 1998; **87**: 921–4

4 Verghese C, Rangasami J, Kapila A, Parke T. Airway control during percutaneous dilatational tracheostomy: pilot study with the intubating laryngeal mask airway. *Br J Anaesth* 1998; **81**: 608–9

5 Parmet JL, Colonna-Romano P, Horrow JC, Miller F, Gonzales J, Rosenberg H. The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult tracheal intubation along with difficult mask ventilation. *Anesth Analg* 1998; **87**: 661–5

6 Rieger A, Brunne B, Hass I, *et al.* Laryngo-pharyngeal complaints following laryngeal mask airway and endotracheal intubation. *J Clin Anesth* 1997; **9**: 42–7

7 Joshi GP, Inagaki Y, White PF, *et al.* Use of the laryngeal mask airway as an alternative to the tracheal tube during ambulatory anesthesia. *Anesth Analg* 1997; **85**: 573–7

8 Cork RC, Depa RM, Standen JR. Prospective comparison of use of the laryngeal mask and endotracheal tube for ambulatory surgery. *Anesth Analg* 1994; **79**: 719–27

9 Keller C, Brimacombe J, Agrò F, Margreiter J. A pilot study of pharyngeal pulse oximetry with the laryngeal mask airway: a comparison with finger oximetry and arterial saturation measurements in healthy anesthetized patients. *Anesth Analg* 2000: **90**: 440–4

10 Brimacombe J, Berry A. The incidence of aspiration associated with the laryngeal mask airway: a meta-analysis of published literature. *J Clin Anesth* 1995; **7**: 297–305

11 Verghese C, Brimacombe J. Survey of laryngeal mask airway usage in 11,910 patients: safety and efficacy for conventional and nonconventional usage. *Anesth Analg* 1996; **82**: 129–33

12 Brimacombe J. The advantages of the LMA over the tracheal tube or facemask: a meta-analysis. *Can J Anaesth* 1995; **42**: 1017–23

13 Ferrari LR, Goudsouzian NG. The use of the laryngeal mask airway in children with bronchopulmonary dysplasia. *Anesth Analg* 1995; **81**: 310–3

14 Keller C, Brimacombe J. Bronchial mucus transport velocity in paralyzed anesthetized patients: a comparison of the laryngeal mask airway and cuffed tracheal tube. *Anesth Analg* 1998; **86**: 1280–2

15 Macario A, Chang PC, Stempel DB, Brock-Utne JG. A cost analysis of the laryngeal mask airway for elective surgery in adult outpatients. *Anesthesiology* 1995; **83**: 250–7

16 Weiler N, Latorre F, Eberle B, Goedecke R, Heinrichs W. Respiratory mechanics, gastric insufflation pressure, and air leakage of the laryngeal mask airway. *Anesth Analg* 1997; **84**: 1025–8

17 Devitt JH, Wenstone R, Noel AG, O'Donnell MP. The laryngeal mask airway and positive-pressure ventilation. *Anesthesiology* 1994; **80**: 550–5

18 Ho-Tai LM, Devitt JH, Noel AG, O'Donnell MP. Gas leak and gastric insufflation during controlled ventilation: face mask versus laryngeal mask airway. *Can J Anaesth* 1998; **45**: 206–11

19 Keller C, Sparr HJ, Luger TJ, Brimacombe J. Patient outcomes with positive pressure versus spontaneous ventilation in non-paralysed adults with the laryngeal mask. *Can J Anaesth* 1998; **45**: 564–7

20 Brimacombe J. Positive pressure ventilation with the size 5 laryngeal mask. *J Clin Anesth* 1997; **9**: 113–7

21 Asai T, Murao K, Yukawa H, Shingu K. Re-evaluation of appropriate size of the laryngeal mask airway. *Br J Anaesth* 1999; **83**: 478–9

22 Maltby JR, Beriault MT, Watson NC, Fick GH. Gastric distension and ventilation during laparoscopic cholecystectomy: LMA-Classic vs. tracheal intubation. *Can J Anaesth* 2000; **47**: 622–6

23 McCrory CR, McShane AJ. Gastroesophageal reflux during spontaneous respiration with the laryngeal mask airway. *Can J Anaesth* 1999; **46**: 268–70

24 El Mikatti N, Luthra AD, Healy TEJ, Mortimer AJ. Gastric regurgitation during general anaesthesia in different positions with the laryngeal mask airway. *Anaesthesia* 1995; **50**: 1053–5

25 Valentine J, Stakes AF, Bellamy MC. Reflux during positive pressure ventilation through the laryngeal mask. *Br J Anaesth* 1994; **73**: 543–4

26 Brain AIJ, Brimacombe JR, Berry AM, Verghese C. Reflux during positive pressure ventilation via the laryngeal mask airway? *Br J Anaesth* 1995; **74**: 489–90

27 Agrò F, Brimacombe J, Verghese C, Carassiti M, Cataldo R. Laryngeal mask airway and incidence of gastro-oesophageal reflux in paralysed patients undergoing ventilation for elective orthopaedic surgery. *Br J Anaesth* 1998; **81**: 537–9

28 Bapat PP, Verghese C. Laryngeal mask airway and the incidence of regurgitation during gynecological laparoscopies. *Anesth Analg* 1997; **85**: 139–43

29 Owens TM, Robertson P, Twomey C, Doule M, McDonald N, McShane AJ. The incidence of gastroesophageal reflux with the laryngeal mask: a comparison with the face mask using esophageal lumen pH electrodes. *Anesth Analg* 1995; **80**: 980–4

30 Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology* 1993; **78**: 56–62

31 Griffin RM, Hatcher IS. Aspiration pneumonia and the laryngeal mask airway. *Anaesthesia* 1990; **45**: 1039–40

32 Nanji GM, Maltby JR. Vomiting and aspiration pneumonitis with the laryngeal mask airway. *Can J Anaesth* 1992; **39**: 69–70

33 Ismail-Zade IA, Vanner RG. Regurgitation and aspiration of gastric contents in a child during general anaesthesia using the laryngeal mask airway. *Paediatr Anaesth* 1996; **6**: 325–8

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BJA

CLINICAL INVESTIGATIONS

Clinical evaluation of circulating blood volume in critically ill patients—contribution of a clinical scoring system†

F. Stéphan[1*], A. Flahault[2], N. Dieudonné[1], J. Hollande[1], F. Paillard[3] and F. Bonnet[1]

[1]Service d'Anesthésie-Réanimation chirurgicale, [2]Antenne de Biostatistiques et d'Informatique médicale and [3]Laboratoire des Explorations Fonctionnelles, Hôpital Tenon, 4 rue de la Chine, F-75970 Paris Cedex 20, France

**Corresponding author*

The circulating blood volume (CBV) of critically ill patients may be difficult to estimate on the basis of history and physical examination. The aim of this study was to evaluate the ability of seven clinical signs and central venous pressure (CVP) to predict CBV in critically ill patients; CBV was evaluated with the [^{125}I]human serum albumin technique. A scoring system was constructed using a combination of independence Bayes method and logistic regression. Sixty-eight patients constituted a 'model development' sample and 30 patients a validation sample. Thirty-six patients (53%) in the model development sample were found to have a low CBV (measured CBV at least 10% lower than the predicted mean normal CBV). Neither the haemodynamic variables monitored in ICU, nor the spot urinary sodium concentrations were different between patients with and without a low CBV. Individually, none of the clinical signs tested have a good positive or negative predictive value. For CVP, only extreme values seem to have clinical significance. To construct the score, the signs tested were ranked according to their discriminating efficacy. The probability of a low CBV was obtained by adding the weights of each sign tested and converting the score obtained into a probability. On a validation sample of 30 patients, the predictions are reliable as assessed by Z statistics ranging between –2 and +2. Our results suggest that: (1) individually, no clinical sign presented a clinical useful predictive value; and (2) a clinical scoring system may be helpful for the evaluation of CBV in critically ill patients.

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Direct measurement of circulating blood volume (CBV) is currently of interest for improving patient care,[1 2] as CBV is distinct from all other haemodynamic variables and is related to preload. Volume-deficit hypovolaemia has been associated with a significant increase in morbidity and mortality.[3] On the other hand, fluid overload is deleterious in patients with acute respiratory distress syndrome.[4] Circulating blood volume monitoring may help to identify such a volume deficit or excess and act as a guide for fluid therapy. However, even nowadays, CBV determination is complex, labour-intensive and time-consuming. Therefore, a reliable clinical evaluation of CBV would be most useful. However, volume-deficit hypovolaemia is quite difficult to detect on the basis of history, urine volumes, sodium concentration or physical examination,[5–8] with a 50% incidence of false-negative results.[6 7] Moreover, in critically ill patients hospitalized for many days, complete examination is often unhelpful or impractical and renal function is rarely preserved.

Clinical evaluation of CBV could encounter two potential problems. First, knowing absolute CBV is less important than the *effective* CBV in determining pre-load responsive-

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ness or in defining the determinants of a particular haemodynamic state. For the physician, hypovolaemia means low pre-load, not just low CBV. Circulating blood volume is one of the most important factors that affect heart pre-load; changes in the compliance of veins maintain the correct relationship between vascular space and CBV.[2 9] Second, the clinical signs used are really aimed at measuring total body 'extracellular' volume which includes intravascular volume and interstitial volume, and therefore, one would not expect them to closely predict intravascular volume.

The aim of this study was to evaluate the ability of the routine clinical parameters used to estimate fluid volume status to predict CBV, and to compare with measurements of CBV using the $[^{125}\mathrm{I}]$albumin technique. The study was divided into two parts: first, clinical variables that best discriminated between patients with and without low CBV were determined; and second, a scoring system which combines elements of Bayes's theorem with those of logistic regression was constructed and prospectively assessed in another group of patients.

Patients and methods

Study population

Our institution's clinical investigation review board approved the study procedure, and informed consent was obtained from each patient or their relatives.

The patient population consisted of subjects admitted to our ICU during a 2-yr period between January 1996 and December 1997, in whom clinical assessment of CBV status had to be confirmed by laboratory measurement, because, after several days in the ICU, the physician was uncertain about the CBV status. Bedside CBV determination is readily available at our institution. The initial study population consisted of 68 patients and represented the model development sample from which the prediction system was derived. Another 30 patients were then included to constitute the test data set. The main reasons for admission to ICU included 39 post-operative cases (orthopaedic, thoracic, vascular and abdominal surgery); 45 cases of sepsis as previously defined,[10] six cases of gastrointestinal haemorrhage and eight miscellaneous causes.

The following information was recorded: age, sex, height and usual weight, new Simplified Acute Physiology Score (SAPS II),[11] duration of ICU stay, time of CBV determination after ICU admission, need for mechanical ventilation or vasoactive drugs, and mortality in ICU.

Clinical assessment of extracellular fluid volume

Each patient underwent two independent physical examinations by two attending physicians before CBV determination. Results of these examinations were subsequently compared. When a disagreement occurred, a third physician was required to make final decision. A chest x-ray was available for all patients. According to previous reports and guidelines,[6 12 13] clinical examination paid special attention to seven signs readily available at the bedside: (1) presence or absence of fluid losses since ICU admission (chest and abdominal drainage, aspiration of gastric contents); (2) fluid balance in the last 24 h by recording intake and output (positive fluid balance if above 400 ml); (3) skin mottling; (4) presence of pulmonary congestion based on detection of pulmonary rales and crackles on physical examination, and/or alveolar oedema and pulmonary vasculature redistribution on chest x-ray; (5) presence of congestive heart failure supported by a past medical history, cardiac enlargement and pulmonary oedema on physical and chest x-ray examination, and gallop rhythm; (6) peripheral oedema; and (7) detection of an enlarged third space: ascites (bulging flanks, fluid wave, shifting dullness), and pleural effusion (dullness on physical examination, compatible chest x-ray). The following variables were also recorded: systolic and diastolic arterial pressure, heart rate, temperature, urine output over the last 24 h, plasma and urinary sodium concentrations, serum total proteins, haemoglobin and haematocrit values.

Central venous pressure (CVP) was measured with a pressure transducer (PVB, Kirchsceon, Germany). Pressures were obtained after calibration, zeroing to atmospheric pressure and using the mid-chest level as reference. Transducers were connected to bedside amplifiers (HP M10469102B, Hewlett Packard). Central venous pressure was recorded at end-expiration.

Circulating blood volume determination

Measurement of CBV was performed with $[^{125}\mathrm{I}]$human serum albumin (SERALB-125®; CIS bio international, Gyf sur Yvette, France) and CBV equipment (Volumetron®; AMES Co, Div. Miles Lab. Inc.; Elkhart, IN, USA), which automatically calculated the volume from the radioactivity injected and from the radioactivity of a post-injection whole blood sample, as previously described.[5]

SERALB-125® was supplied as a sterile solution of human serum albumin labelled with iodine ^{125}I, made isotonic with sodium chloride. The radioactive concentration was 185 kBq ml^{-1} (5 μCi ml^{-1}) at the calibration date; SERALB-125® contains 9 mg of human serum albumin ml^{-1}. Not less than 97% of the total radioactivity was bound to human serum albumin. After treatment any acute episode of severe hypotension, 3.5 μCi of SERALB-125® were injected i.v. (# 0.7 ml of solution). The radioactivity injected was assumed to be the difference of the activities contained in the syringe before and after injection. Blood was withdrawn from a vein of the contralateral arm after 10 min, as previously recommended.[5] The concentration of test substance in the sample was obtained from simultaneous measurements of fixed volumes of pre-mixing and post-mixing blood samples.

Plasma volume and cell volume were calculated from CBV and peripheral haematocrit corrected for the body-to-venous haematocrit ratio (0.91). Interpretation of results was based on comparison between observed values and expected values in healthy subjects of the same sex, height, weight and age. The expected values for healthy subjects have been previously reported.[14 15] Precision of CBV determination is ±5% (Dr F. Paillard, personal communication). Hypovolaemia was defined as a CBV at least 10% lower than the predicted mean normal CBV.

Statistical analysis

Hypovolaemic and non-hypovolaemic patients were compared using the chi-squared test or Fisher's exact test for categorical variables, and Student's t- or Mann–Witney U-test for continuous variables. A two-sided formulation with a P value <0.05 was required for statistical significance. Results are expressed as mean (SD) for continuous variables, and as per cent for categorical variables.

Agreement between physicians on the presence or absence of a clinical sign was assessed by the kappa measurement of agreement.[16] Kappa values exceeding 0.75 represent excellent agreement, values between 0.4 and 0.75 indicate fair to good agreement, and values less than 0.4 indicate poor agreement.[16]

Standard formulas were used to calculate sensitivity (true positives/[true positives+false negatives]), specificity (true negatives/[true negatives+false positives]), positive predictive value (true positives/[true positive+false positives]), and negative predictive value (true negative/[true negatives+false negatives]) for each clinical parameter.[17]

To decide the optimum cut off point for CVP, a Receiver Operating Characteristics (ROC) curve was constructed, which plots true- and false-positives rates (sensitivity and 1 minus specificity, respectively) for a series of cut off points.[17]

Calculation of Spiegelhalter–Knill-Jones weightings

Many statistical methods have been developed to improve the physician's judgment. Over the past few years, Spiegelhalter and Knill-Jones have proposed a simple scoring system which adds precision to risk assessment in individual patients.[18 19] This statistical method combines elements of Bayes' theorem with those of logistic regression. The result is a system that neatly sidesteps some of the main disadvantages of the two original techniques. For example, it does not assume that all risk factors are acting independently within each outcome class (the 'independence Bayes' assumption, which is central to many bayesian analyses) because an adjustment is made, while at the same time predictions are presented in a form which is less mathematical and much more clinically relevant than the output of a conventional logistic regression analysis. Another reason why this method may be preferred over simple logistic regression is the ability to integrate zero for missing data. Finally, the weights of evidence may be viewed as tools for refining risk prediction by taking into account key clinical parameters in the individual patient. Once the Spiegelhalter–Knill-Jones weightings have been derived they can be used by the non-mathematician, but the process of derivation from the training data set requires statistical skill (see Appendix). The Spiegelhalter–Knill-Jones scoring system, applied to the evaluation of CBV could, therefore, improve the physician's clinical judgment.

Validation of the clinical scoring system

The predictive accuracy of the Spiegelhalter and Knill-Jones weighting system was measured in the 30 patients constituting the test data set. The predictive probabilities have been grouped into four categories and the *observed* number of hypovolaemic patients (O) in each category is noted. The four categories are defined according to the range of probabilities of expected hypovolaemia: category 1, 0–10%; category 2, 11–49%; category 3, 50–70%; and category 4, 71–100%.

The *expected* number of hypovolaemic patients (E), assuming the prediction is completely reliable, is also shown. According to the null hypothesis that the predictions are reliable, O would be approximately distributed with the mean E and a standard error (SE) equal to $[E(1-E/n)]^{1/2}$. Hence, $Z=(O-E)/(\mathrm{SE})$ will be approximately a standard normal statistic according to the null hypothesis of perfect reliability. Values of Z greater than 2 suggest that the 'probability' attributed to hypovolaemia is too low, while values of Z less than -2 suggest that the probabilities are too high.[19]

Results

Clinical characteristics of initial study population and CBV determination

The clinical characteristics of the 68 patients, with and without hypovolaemia according to CBV determination, are shown in Table 1. In the model development sample, 36 patients were classified as hypovolaemic (53%). Results of CBV determination for the two groups are summarized in Table 1.

Diagnostic value of laboratory parameters and haemodynamic measurements

Results are presented in Table 2. Neither the haemodynamic parameters usually monitored in ICU, nor the spot urinary sodium concentrations were different between hypovolaemic and non-hypovolaemic patients. However, serum total protein and haemoglobin concentrations were higher in hypovolaemic patients.

Agreement between physicians and accuracy of each clinical parameter

Agreement between physicians was excellent for the elicited physical signs. Kappa values were 0.78 for the presence or absence of pulmonary congestion; 0.82 for the presence or absence of peripheral oedema; 0.84 for the presence or absence of congestive heart failure; 0.86 for detection or absence of third spacing; and 1.00 for the presence or absence of skin mottling.

The accuracy of each of the seven clinical signs in the model development sample is shown in Table 3. Sensitivity was 0.94 for absence of congestive heart failure, which was marginally higher than the sensitivity of absence of pulmonary oedema or absence of third spacing (both equal to 0.92). Specificity was highest for the presence of fluid losses and presence of skin mottling (both equal to 0.78), and lowest for absence of third spacing (0.19). Positive predictive value was highest for the absence of peripheral oedema (0.62). Negative predictive value was highest for the presence of skin mottling (0.49), closely followed by the presence of fluid losses (0.48).

Calculation of Spiegelhalter–Knill-Jones weightings and application to individual patients

Table 4 gives the starting score and adjusted weights of evidence needed to predict the chances of hypovolaemia from the seven clinical signs and CVP measurement. The goodness of fit of the stepwise logistic regression was 0.51.

The cut off value for CVP was obtained from the upper left corner of the ROC curve. For a cut off value of CVP <2 mm Hg, the sensitivity was 0.38 and the specificity was 0.84 (data not shown).

Two steps are required to predict the risk of hypovolaemia in an individual patient. First, by referring to Table 4, the starting score is added to the appropriate adjusted weights of evidence for that patient. Then, by referring to Figure 1, the total score obtained is converted into a probability of hypovolaemia. These steps are illustrated in the following example. A patient presented with septic shock after cholangitis. Three days after ICU admission, physical examination showed peripheral oedema, fluid losses, and a negative fluid balance. No signs of pulmonary congestion, congestive heart failure, skin mottling, or

Table 1 Clinical characteristics and blood volume estimations by the radioiodine-labelled human serum albumin technique in hypovolaemic and non-hypovolaemic patients. **P* values are reported when <0.2, otherwise non-significant (NS). Definitions of abbreviations: SAPS II=simplified acute physiology score; BV=blood volume. Values are expressed as mean (SD)

	Hypovolaemic (*n*=36)	**Non-hypovolaemic (*n*=32)**	***P* value***
Reasons for ICU admission			0.18
Post-operative cases (%)	47	28	
Sepsis (%)	36	63	
Gastrointestinal haemorrhage (%)	8.5	6	
Miscellaneous causes (%)	8.5	3	
Age (yr) (range)	61 (35–88)	66 (18–89)	0.18
Sex, male/female	24/12	22/10	NS
SAPS II score	36 (16)	41 (21)	NS
Temperature (°C)	37.3 (0.9)	37.2 (1.0)	NS
Need for mechanical ventilation (%)	69	31	0.002
Need for vasoactive drugs (%)	44	19	0.03
Duration of ICU stay (days)	13 (20)	13 (13)	NS
Mortality (%)	25	31	NS
Time of BV determination after ICU admission (days)	3.5 (6)	4.6 (4.7)	NS
Blood volume (ml)	3350 (590)	4089 (1176)	0.001
Blood volume excess or deficit	–514 (194)	88 (273)	<0.0001
Index (ml m^{-2})	range –236, –111	range –234, +806	
Blood volume, relative change (%)	–22 (8)	4 (12)	<0.0001
Venous haematocrit (%)	33.5 (7.0)	29.6 (3.9)	0.006

Table 2 Haemodynamic and laboratory variables between hypovolaemic and non-hypovolaemic patients. **P* values are reported when <0.2, otherwise non-significant (NS) is state. †Spot urinary sodium concentration was included only for 47 patients without diuretic treatment (24 hypovolaemic and 23 non-hypovolaemic patients). Values are expressed as mean (SD)

	Hypovolaemic (*n*=36)	**Non-hypovolaemic (*n*=32)**	***P* value***
Heart rate (beats min^{-1})	103 (18)	102 (16)	NS
Systolic arterial pressure (mm Hg)	124 (23.4)	120 (20.0)	NS
Diastolic arterial pressure (mm Hg)	68 (17.5)	62 (13.0)	0.11
Urine output over the last 24 h (ml)	1620 (1013)	1593 (769)	NS
Plasma Na^{+} (mmol litre^{-1})	135 (5.5)	137 (5.0)	NS
Spot urinary Na^{+} (mmol litre^{-1})†	68 (42)	63 (38)	NS
Serum total protein (g litre^{-1})	39 (12)	34 (8)	<0.05
Haemoglobin (g dl^{-1})	11.5 (2.7)	9.6 (1.2)	0.002

increased third space was found. Central venous pressure could not be measured. The adjusted weights of evidence for pulmonary congestion (+20), peripheral oedema (–29), skin mottling (–10), congestive heart failure (+11), third spacing (+27), fluid losses (+14), fluid balance (+41), and CVP (0) were added to the starting score (–5 in every case) (Table 4). The total score was +74. A total score of +74 corresponds to a predicted probability of hypovolaemia of 70% (Fig. 1).

Predictive accuracy of the Spiegelhalter–Knill-Jones scoring system

The Spiegelhalter–Knill-Jones scoring system was tested on a prospective series of 30 patients. This population of patients was comparable with the training data set in terms of sex ratio, need for mechanical ventilation, main reasons for ICU admission, SAPS II score (mean 39 (SD 12) *vs* 39 (18)), and time of CBV determination after ICU admission (4 (3) *vs* 4 (5) day).

Figure 2 gives the reliability of adjusted predictions. The percentage of hypovolaemia observed in patients in the test data set is plotted against the percentage of hypovolaemia expected from the calculated predictions. The line produced is close to the line of identity. The results indicate that the predicted probabilities are reliable, especially for patients with a high probability—that is, patients predicted to have, say 60% chance of hypovolaemia will actually have hypovolaemia about 60% of the time.

Discussion

Our study demonstrates that the usual haemodynamic parameters monitored in ICU and spot urinary sodium concentration are unreliable in differentiating patients with

Table 3 Accuracy of the seven clinical variables used to predict hypovolaemia

Clinical variable	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Presence of fluid losses	0.25	0.78	0.56	0.48
Negative fluid balance	0.44	0.71	0.61	0.39
Presence of skin mottling	0.28	0.78	0.59	0.49
Absence of peripheral oedema	0.64	0.56	0.62	0.38
Absence of pulmonary oedema	0.92	0.31	0.60	0.40
Absence of third spacing	0.92	0.19	0.56	0.44
Absence of congestive heart failure	0.94	0.20	0.58	0.44

Table 4 Crude weights for symptoms of hypovolaemia and normo/hypervolaemia, and effect of adjustment of crude scores by logistic determination. The goodness of fit chi-square of this model remained non-significant during the eight steps (P=0.51 at the last step). †Third spacing: ascites, pleural effusion. ‡Available for 63 patients only; value of fluid excess was 1553 (1154) ml (range 400–5840) and value of fluid deficit was –946 (1018) ml (range 230–3990). §Central venous pressure was measured in 65 patients only. LR: likelihood ratio

Symptom	Hypovolaemic (n=36)	Normo or hypervolaemic (n=32)	LR	Crude weights	Logistic coefficients (SE)	Adjusted weight	Range of adjusted weights
Prior probability	0.53	0.47		12	–5 (1.8)	–5	
Pulmonary oedema							
Yes	3	10	0.27	–131	0.69 (0.9)	–90	110
No	33	22	1.33	29		20	
Peripheral oedema							
Yes	13	18	0.64	–45	0.65 (0.7)	–29	54
No	23	14	1.46	38		25	
Skin mottling							
Yes	10	7	1.27	24	1.22 (0.8)	29	39
No	26	25	0.92	–8		–10	
Congestive heart failure							
Yes	2	5	0.36	–102	1.03 (1.1)	–105	116
No	34	27	1.12	11		11	
Third spacing†							
Yes	3	6	0.44	–82	2.25 (1.3)	–184	211
No	33	26	1.13	12		27	
Fluid losses							
Yes	9	7	1.14	13	1.09 (0.8)	14	18
No	27	25	0.96	–4		–4	
Fluid balance‡							
Positive or nil	18	22	0.79	–24	0.99 (0.7)	–24	65
Negative	14	9	1.51	41		41	
Central venous pressure§							
≤2 mm Hg	13	5	2.37	86	1.36 (0.8)	117	159
>2 mm Hg	21	26	0.74	–31		–42	

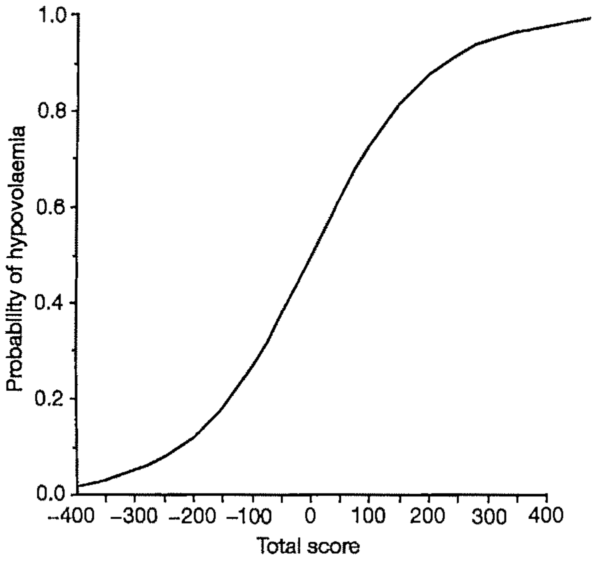

Fig 1 Relationship between hypovolaemia score and its theoretical probability. Probability=1/($e^{-T/100}$+1); Score=100 Ln [probability/(1–probability)].

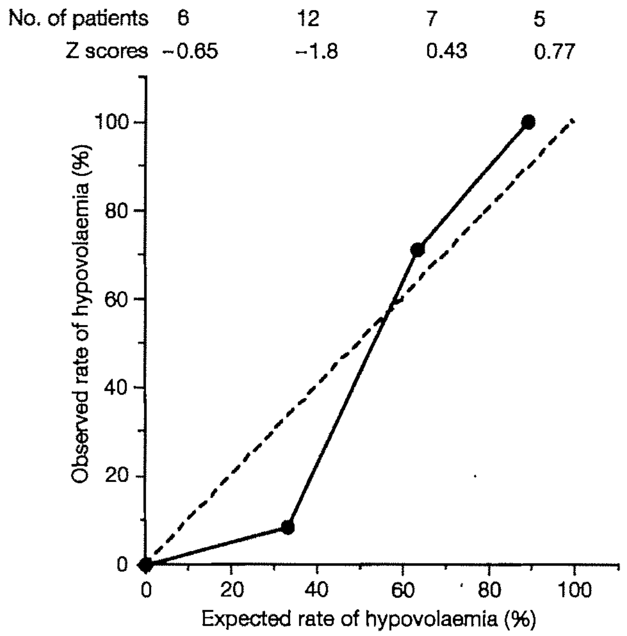

Fig 2 Observed and expected (predicted) rates of hypovolaemia status in test data set (30 ICU patients). A perfect predictor would exactly coincide with the diagonal line running from bottom left to top right (line of identity). As values of Z statistic lie within the range –2 to +2, the fit of the predictor to the line of identity is satisfactory. Predictions are therefore reliable.

and without a low CBV, several days after their ICU admission. However, careful physical examination, resulting in a clinical scoring system, improves the clinical ability to determine the patient's CBV status. Our study design was not addressed to patients with acute illness who became hypotensive in the emergency department or several hours after ICU admission, as these situations are totally different from patients hospitalized for several days in ICU, in whom either large fluid volumes or diuretics may have been recently administered. In such cases, the clinical diagnosis of CBV status constitutes a real challenge for the physician.

We chose the radioactive-labelled albumin method for quantitative CBV determination as the standard. However, using this method in ICU patients raises several problems.[2] First, measurement of CBV depends on adequacy of mixing of [^{125}I]albumin throughout the vascular system and rapid whole body disappearance of the tracer.[20] In the present study, the measurement of CBV 10 min after tracer injection corresponded to the best compromise between complete mixing of the tracer with plasma and its disappearance.[5 21 22] However, despite a close correlation with other techniques,[23] this method could lead to a slight overestimation of CBV.[20 23] Second, septic patients have altered capillary permeability.[24] However, [^{125}I]albumin disappearance rate has been reported to be almost unmodified after endotoxin administration[21] and determination of CBV has been shown to be accurate in septic patients.[25] Third, CBV measurements are commonly compared with predicted CBV values derived from measurements in a normal population. However, the 'normal' values of CBV could be different in critically ill patients. Unfortunately, to our knowledge, there are no published data concerning normal CBV values in critically ill patients. Despite these concerns, direct measurement of CBV by a radioactive tracer in ICU patients has been shown to be accurate and reproducible.[5 25 26]

We have defined hypovolaemia in term of intravascular volume because CBV is one of the most important factors affecting pre-load. In most clinical studies, the term hypovolaemia refers to either volume depletion or dehydration.[8] One could argue that measurement of CBV only refers to intravascular volume and ignores interstitial and intracellular volumes, but it has been demonstrated that CBV correlates well with extracellular fluid volume.[27] Both CBV and vascular capacitance determine the 'effective' CBV. It could, therefore, be hypothesized that septic patients could have an unchanged CBV despite a decreased pre-load. However, Rothe and colleagues reported that, in an endotoxin shock model, CBV decreased by nearly 30% after endotoxin infusion.[21] It has also been shown that 'effective' vascular compliance is already decreased in patients under mechanical ventilation with sepsis syndrome, or when sympathetic nervous system tone is elicited.[9] It could also be argued that the division into hypovolaemia and non-hypovolaemia on the basis of a greater than 10% reduction in the measured CBV could be too stringent. However, the mean CBV deficit was –948 ml in hypovolaemic patients and only two non-hypovolaemic patients overlapped with this threshold.

Previous studies have indicated that clinical estimates of a patient's fluid volume status are not reliably perceived by physical examination alone, with an accuracy range from 30 to 50%.[5–8 28–31] One possible explanation is that physicians do not optimally use clinical information when assessing fluid volume status. [32] In our series, hypovolaemia was present in about one half of ICU patients, as reported by Shoemaker and colleagues using the same method in a comparable patient population.[26] Ourselves and others[25 33] have noted that the use of routine haemodynamic variables are of little value to differentiate hypovolaemic and non-hypovolaemic patients. Likewise, spot urinary sodium concentration is not useful in this setting in contrast with its value in stable, non-critically ill patients.[6] Renal losses of sodium and water are often a result of an osmotic diuresis. One common culprit is glycosuria, but other causes (e.g. post-obstructive diuresis, profuse diuresis during recovery from acute renal failure) may account for such differences. The value of haemoglobin concentration has several limitations. During rapid and severe bleeding, the patients may exsanguinate before transcapillary migration of interstitial fluid can significantly reduce the haemoglobin value. On the other hand, haemoglobin changes become almost uninterpretable when patients have been given large volumes of packed red cells and fluids.

The clinical signs that were used are really aimed at measuring total body 'extracellular' volume and are not directly indicative of intravascular volume. However, there is a relationship between clinical features such as oedema and aspiratory crackles and CBV.[27] On the other hand, the appearance of reduced CBV in the face of expanded extracellular fluid has been described.[26] As a consequence, based on the values of the likelihood ratio and as shown in Table 3, none of these findings is particularly helpful when present in isolation, as previously reported.[8] On the other hand, combinations of physical signs appear to be more helpful.[8] Inspection of the range of adjusted weights given in Table 4 allows comparison of the value of the symptoms. The wider the range of an indicator, the greater its potential value as a diagnostic item. However, it is possible to have a very powerful symptom that is so rarely present that it would not normally be ascertained in clinical evaluation. Central venous pressure was the last variable taken into account in the score, as CVP is commonly measured in critically ill ICU patients.[32] However, we found that only a value <2 mm Hg provided evidence in favour of hypovolaemia. CVP may vary considerably in critically ill patients, because of heart–lung interactions, especially in mechanically ventilated patients,[34] and therefore only extreme values seem to have any clinical significance.

Regarding the Spiegelhalter–Knill-Jones system, three points must be stressed. First, the predictive accuracy of the system appears reliable. However, the system seems to be less reliable for patients with a low probability of hypovolaemia (Figure 2). Second, some cardiopulmonary signs have been suggested to be of questionable reliability.[35 36] However, most of the signs used to construct the system frequently occur in the ICU setting, and unreliability of the signs seems to be linked to their low frequency of appearance.[35 36] Finally, if the criteria of hypovolaemia change, the sensitivity and specificity of each of the signs may be different,[8] affecting the prediction of the model.

Following recent concerns and doubts about the efficacy and safety of using Swan-Ganz catheterization to assess haemodynamic status,[37] there are no guidelines to help the physician to decide when to use or to withhold invasive monitoring in individual patients.[29] We believe the application of such a method could lead to a more judicious selection of diagnostic tests. In conclusion, physicians working in ICU are daily called upon to predict the patient's fluid volume status on the basis of existing symptoms and signs, physical findings, and laboratory results. As illustrated by the Spiegelhalter–Knill-Jones method, a science of clinical prediction has been developed, and it is now possible to make quantitative predictions by using statistical models and to more rigorously assess the accuracy of these predictions.

Appendix

Summary of statistical techniques used to derive Spiegelhalter–Knill-Jones weightings.

(1) Calculation of the likelihood ratio (LR)

To calculate the LR for a given sign, the patients were divided into hypovolaemic and non-hypovolaemic patients. A standard 2×2 table allowed calculation of sensitivity, specificity, and LR for the presence or absence of a given sign:

LR for the presence of a particular sign=sensitivity/(1–specificity)

LR for the absence of a particular sign=(1–sensitivity)/specificity.

(2) Bayes' theorem for calculation of the post-test probability of disease

The independence Bayes equation may be expressed as:

Posterior odds=prior odds×LR of sign 1×LR of sign 2 . . .×LR of sign N (1)

where posterior odds is the predicted odds of hypovolaemia in an individual, and prior odds is the odds of hypovolaemia in the study population.

(3) Converting LR into scores and weights

To convert LR into a simple score that can be added up, we took the natural logarithm of this LR, as the logarithm can be added rather than multiplied, thus simplifying the process. For further simplicity, this value was multiplied by 100 and rounded off so that crude weights could be expressed as whole numbers.

Equation (1) therefore becomes:

100 Ln posterior odds=100 Ln prior odds+100 Ln LR of sign 1+100 Ln LR of sign 2 . . .+100 Ln LR of sign N (2).

By using the terminology of the Spiegelhalter and Knill-Jones method, equation (2) becomes:

Total score (T)=starting score+crude weights of sign 1+crude weights of sign 2 . . .+crude weights of sign N (3).

The starting score reflects the prior probability of hypovolaemia and could be different according to the specificity of the ICU.

(4) Adjustment of crude weights

The use of Bayes theorem could lead to considerable problems in overestimating the probabilities of hypovolaemia, as the assumption of independence of different signs is rarely satisfied in practice. A statistical method of making an adjustment must therefore be defined. The Spiegelhalter and Knill-Jones method calculates 'adjusted weights of evidence', which are obtained by entering the value of the crude weights as independent variables in a logistic regression equation. Data were computerized (Compaq prolinea 575E) and analysed using BMDP statistical packages (BMDP Statistical Software, 7.0 software release 1992; Inc. Los Angeles, CA, USA). Goodness of fit was assessed by the Hosmer and Lemeshow chi-squared test. The resulting regression coefficients a_0, a_1, a_2, a_n are displayed, together with their standard error (SE). After multiplication of crude weights by their respective regression coefficient, equation (3) becomes:

Total score (T)=a_0+adjusted weights of sign 1+adjusted weights of sign 2 . . .+adjusted weights of sign N (4).

(5) Converting scores back to probability of disease

Because T=100 (Ln posterior odds) and because odds=(probability of event)/(1–probability of event), it may be calculated that probability of hypovolaemia (in %)=$(e^{T/100}/1+e^{T/100})\times 100=1/(e^{-T/100}+1)\times 100$. This can be performed more rapidly by using a simple graph.

References

1 Tschaikowsky K, Meisner M, Durst R, Rügheimer E. Blood volume determination using hydroxyethyl starch: A rapid and simple intravenous injection method. *Crit Care Med* 1997; **25**: 599–606

2 Jones JG, Wardrop CAJ. Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth* 2000; **84**: 226–35

3 Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. *Arch Surg* 1973; **106**: 630–6

4 Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Resp Dis* 1992; **145**: 990–8

5 Williams JA, Fine J. Measurement of blood volume with a new apparatus. *N Engl J Med* 1961; **264**: 842–8

6 Chung H-M, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 1987; **83**: 905–8

7 Cook DJ. Clinical assessment of central venous pressure in the critically ill. *Am J Med Sci* 1990; **229**: 175–8

8 McGee S, Abernethy WB, Simel DL. Is this patient hypovolemic? *JAMA* 1999; **281**: 1022–9

9 Stéphan F, Novara A, Tournier B, *et al.* Determination of total effective vascular compliance in patients with sepsis syndrome. *Am J Respir Crit Care Med* 1998; **157**: 50–6

10 American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee. Definitions for sepsis and organ failures and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74

11 Le Gall J-R, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957–63

12 Brezis M, Rosen S, Epstein KH. Acute renal failure. In: Brenner BM, Rector Jr FC eds. *The Kidney*, 4th edn. Philadelphia: WB Saunders Company, 1991; 993–1061

13 Greco BA, Jacobson HR. Fluid and electrolyte problems with surgery, trauma, and burns. In: Koko JP, Tannen RL, eds. *Fluids and Electrolytes*, 3rd edn. Philadelphia: WB Saunders Company, 1996; 729–58

14 Wennesland R, Brown E, Hopper J, *et al.* Red cell, plasma and blood volume in healthy men measured by radiochromium cell tagging and hematocrit: influence of age, somatotype and habits of physical activity on the variance after regression of volumes to height and weight combined. *J Clin Invest* 1959; **38**: 1065–77

15 Brown E, Hopper J, Hodges JL, Bradley B, Wennesland R, Yamauchi H. Red cell, plasma, and blood volume in healthy women measured by radiochromium cell-labelling and hematocrit. *J Clin Invest* 1962; **41**: 2182–90

16 Armitage P, Berry G. *Statistical Methods in Medical Research*, 6th edn. Oxford: Blackwell Scientific Publications, 1994

17 Griner PF, Mayewski RJ, Mushlin AI, Greenland P. Selection and interpretation of diagnostic tests and procedures. Principles and applications. *Ann Intern Med* 1981; **94**: 553–600

18 Spiegelhalter DJ, Knill-Jones RP. Statistical and knowledge-based approaches to clinical decision-support system, with an application in gastroenterology. *J R Statist Soc A* 1984; **147**: 35–77

19 Spiegelhalter DJ. Probabilistic prediction in patient management and clinical trials. *Stat Med* 1986; **5**: 421–33

20 Bent-Hansen l. Initial plasma disappearance and distribution volume of ^{131}I-albumin and ^{125}I-fibrinogen in man. *Acta Physiol Scand* 1989; **136**: 455–61

21 Rothe CF, Murray RH, Bennett TD. Actively circulating blood volume in endotoxin shock measured by indicator dilution. *Am J Physiol* 1979; **236**: H291–H300

22 Payen J-F, Vuillez J-P, Geoffray B, *et al.* Effects of preoperative intentional hemodilution on the extravasation rate of albumin and fluid. *Crit Care Med* 1997; **25**: 243–8

23 Thomsen JK, Fogh-Andersen N, Bülow K, Devantier A. Blood and plasma volumes determined by carbon monoxide gas, ^{99m}Tc-labelled erythrocytes, ^{125}I-albumin and the T^{1824} technique. *Scand J Clin Lab Invest* 1991; **51**: 185–90

24 Ellman H. Capillary permeability in septic patients. *Crit Care Med* 1984; **12**: 629–33

25 Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; **12**: 107–12

26 Shoemaker WC, Bryan-Brown CW, Quigley L, Stahr L, Elwyn DH, Kark AE. Body fluid shifts in depletion and poststress states and their correction with adequate nutrition. *Surg Gynecol Obstet* 1973; **136**: 371–4

27 Bogaard HJ, de Vries JPPM, de Vries PMJM. Assessment of refill and hypovolaemia by continuous surveillance of blood volume and extracellular fluid volume. *Nephrol Dial Transplant* 1994; **9**: 1283–7

28 Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984; **12**: 549–553

29 Connors AF Jr, Dawson NV, Shaw PK, Montenegro HD, Nara AR, Martin L. Hemodynamic status in critically ill patients with and without acute heart disease. *Chest* 1990; **98**: 1200–6

30 Steingrub JS, Celoria G, Vickers-Lahti M, Teres D, Bria W. Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. *Chest* 1991; **99**: 1451–5

31 Mimoz O, Rauss A, Rekik N, Brun-Buisson C, Lemaire F, Brochard L. Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. *Crit Care Med* 1994; **22**: 573–9

32 Connors AF, Dawson NV, McCaffree DR, Gray BA, Siciliano CJ. Assessing hemodynamic status .in critically ill patients: do physicians use clinical information optimally? *J Crit Care* 1987; **2**: 174–80

33 Lazrove S, Waxman K, Shippy C, Shoemaker WC. Hemodynamic, blood volume, and oxygen transport responses to albumin and hydroxyethyl starch infusions in critically ill postoperative patients. *Crit Care Med* 1980; **8**: 302–6

34 Pinsky MR. The hemodynamic consequences of mechanical ventilation: An evolving story. *Intensive Care Med* 1997; **23**: 493–503

35 Koran LM. The reliability of clinical methods, data and judgments (first of two parts). *N Engl J Med* 1975; **293**: 642–6

36 Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. *Lancet* 1988; **i**: 873–5

37 Connors A, Speroff T, Dawson N, Thomas C, Knauss W. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; **276**: 889–97

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Recovery after remifentanil and sufentanil for analgesia and sedation of mechanically ventilated patients after trauma or major surgery

S. Soltész[1]*, A. Biedler[1], M. Silomon[1], I. Schöpflin[1] and G. P. Molter[2]

[1]*Klinik für Anaesthesiologie und Intensivmedizin, Universitätskliniken des Saarlandes, D-66421 Homburg, Germany.* [2]*Klinik für Anaesthesiologie und operative Intensivmedizin, Klinikum Leverkusen, Dhünnberg 60, D-51375 Leverkusen, Germany*

**Corresponding author*

We investigated the analgesic effect and the neurological recovery time after administration of remifentanil in mechanically ventilated patients in an intensive care unit. Twenty patients, after trauma or major surgery with no intracranial pathology, were randomized to receive either remifentanil/propofol (n=10) or sufentanil/propofol (n=10). A sedation score and a simplified pain score were used to assess adequate sedation and analgesia. Medication was temporarily stopped after 24 h. Immediately before and 10 and 30 min after, the degree of sedation and pain score were evaluated. Adequate analgesia and sedation was achieved with remifentanil 10.6 μg kg^{-1} h^{-1} and propofol 2.1 mg kg^{-1} h^{-1}, or sufentanil 0.5 μg kg^{-1} h^{-1} and propofol 1.3 mg kg^{-1} h^{-1}. The difference in propofol dose between groups was significant. Ten minutes after terminating the medication, the degree of sedation decreased significantly after remifentanil and all patients could follow simple commands. During the following 20 min, all patients with remifentanil emerged from sedation and complained of considerable pain. By contrast, in the sufentanil group, only six (7) responded to commands after 10 (30) min and their pain score remained essentially unchanged during the 30-min observation period. We conclude that, in contrast to sufentanil, remifentanil facilitates rapid emergence from analgesia and sedation, allowing a clinical neurological examination within 10–30 min in mechanically ventilated patients with no intracranial pathology.

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Effective pain control is essential for optimal care of patients after trauma and surgery.[1 2] Thus, in most intensive care units (ICU) analgesia as well as sedation is provided to enable the patient to tolerate the tracheal tube and mechanical ventilation. Accumulation of long-acting opioids occurs, and continuous assessment and adjustment of dose to meet the changing need is necessary. In addition, emergence from analgesia and sedation in patients with impaired liver or kidney function may be significantly prolonged. An intermittent neurological assessment of patients with brain injury may be difficult

As remifentanil is metabolized by non-specific esterases, it is eliminated very quickly and independently of liver or kidney function. The context-sensitive half time is 3–4 min and is independent of the duration of infusion.[3]

The present investigation was performed to study the effects of remifentanil administered in combination with a hypnotic to provide analgesia and sedation in ICU patients. We wanted to investigate if it was possible to: (1) provide adequate analgesia with remifentanil and (2) achieve complete emergence from analgesia and sedation (neurological recovery) within minutes after termination of the remifentanil infusion. As morphine and fentanyl[4] have unfavourable pharmacokinetics if administered as a continuous infusion, we chose sufentanil for comparison with remifentanil. Sufentanil has a context-sensitive half time of

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Table 1 Individual patient characteristics. M=male, F=female, R=remifentanil, S=sufentanil

Age (yr)	Weight (kg)	M/F	R/S	Disease	Type of operation	Fentanyl before trial (mg h^{-1})	Midazolam before trial (mg h^{-1})	Analgosedation before trial (h)
45	90	M	R	Haematothorax, pneumothorax, multiple rib fractures	–	0.23	5	3
19	60	M	R	Pneumothorax, maxillary and zygomatic bone fractures	–	0.0625	3.75	24
36	80	M	R	Lung contusion, ulnar fracture, orbital fracture, aspiration,	–	0.2	3	6.5
51	80	M	R	Lung contusion, maxillary fracture, tibial shaft fracture	Tibial shaft osteosynthesis	1.1	11	2
40	60	M	R	Palatine carcinoma	Tumor excision, neck dissection	0.04	2	5
83	85	M	R	Cheilocarcinoma	Mandibular resection, neck dissection	0.08	5.2	5
29	90	M	R	Peritonsillar abscess	Incision	0.06	3.5	26
45	84	M	R	Oral carcinoma	M. latissimus dorsi flap	0.075	1.1	12
58	79	M	R	Oral carcinoma	Free flap, neck dissection	0.09	0.36	11
39	80	F	R	Oral carcinoma	Resection, neck dissection	0.1	2	5
28	90	M	S	Haematothorax, pneumothorax, multiple BWS and LWS fractures	–	0.09	5.1	15
48	90	M	S	Thorax trauma, acetabular fracture	–	0.3	6	5
37	80	M	S	Lung contusion, haematothorax, pneumothorax	–	0.2	1.7	3
49	80	M	S	Multiple rib fractures, abdominal trauma, pelvic fracture	Laparotomie, exitus	0.3	5	2
48	80	M	S	Facial gunshot wound	Reconstruction, free flap	0.074	–	9.5
65	40	F	S	Terminal enteritis, colon perforation	Left hemicolectomy, lavage	0.2	3.1	3.5
50	95	M	S	Oral carcinoma	Tumour excision, neck dissection	0.06	2.5	10
61	50	F	S	Oral carcinoma	Tumour excision, neck dissection	0.16	2.2	4.5
58	75	M	S	Oral carcinoma	Tumour excision, neck dissection	0.12	2.7	7.5
38	81	M	S	Carcinoma of tongue	Resection, neck dissection	0.08	2	7.5
69	65	F	S	Alveolar process carcinoma	Mandibular resection, neck dissection	0.13	2.7	5

34 min after 4 h infusion.[3] Since its introduction in the 1980s, sufentanil has been frequently used for postoperative analgesia and sedation in ICU patients.[5–8]

Methods

After approval by the Ethics Committee and written informed consent from the patient (elective surgery) or relatives (trauma), 21 mechanically ventilated patients requiring analgesia and sedation were included in the study. Indications for mechanical ventilation were respiratory failure after major trauma or operation, or compromised airways because of infection or postoperative swelling. The design of the investigation was double blind and prospective. Patients were assigned randomly to group R (remifentanil) or S (sufentanil) using a computerized allocating schedule. Exclusion criteria were: age <18 yr, pregnancy, neurological disease (history of apoplectic stroke, severe head trauma), coronary artery disease CCS III-IV (Canadian Cardiovascular Society), congestive heart failure NYHA III-IV (New York Heart Association), unstable haemodynamics (patients requiring >4 units of blood or 2 litre of cristalloids or colloids in 12 h in addition to basic fluid replacement; patients requiring cardiocirculatory support of dopamine >3 μg kg^{-1} min^{-1} or norepinephrine >0.1 μg kg^{-1} min^{-1}), intolerance to one of the used drugs, hepatic or renal abnormalities (serum cholinesterase <10 000 nkat litre^{-1}, serum bilirubin >24 μmol litre^{-1}; serum creatinine >100 μmol litre^{-1}).

Patients received either balanced anaesthesia with isoflurane, nitrous oxide, and fentanyl in the operating theatre (elective surgery) or a fentanyl/midazolam anaesthesia in the emergency room (trauma). On transfer to and after arrival at the ICU, all patients received midazolam and fentanyl before the trial was started. Details of the patients and the amounts of fentanyl and midazolam administered before the onset of the trial are listed in Table 1. For every patient, the study started during the first 24 h of their study on the ICU.

To evaluate the degree of sedation, we used the Ramsay score.[9] In order to assess pain, we used a simplified pain score, which allowed the sedated patient (Ramsay score 2–5) to differentiate between three levels of pain: (1) nodding the head for 'I feel pain', (2) shaking the head for 'I don't feel pain', and (3) no head movement because of marked sedation (Ramsay >3). As far as possible, under the clinical conditions of a critically ill patient requiring high amounts both sedative and analgesic drugs, we tried to differentiate between insufficient sedation and incomplete pain relief.

Propofol was administered with an initial dose of 2 mg kg^{-1} h^{-1} as the sedative component. In addition, patients initially received either remifentanil 5 μg kg^{-1} h^{-1} or sufentanil 0.5 μg kg^{-1} h^{-1}. The aim was to achieve a Ramsay score adapted to the patient's individual demand ranging from 2 (e.g. weaning from artificial ventilation) to 5 (e.g. in case of severe respiratory failure) together with complete pain relief. In case of pain or inadequate sedation, the dose of the drugs was adjusted stepwise according to the following procedure.

In case of inadequate sedation, the propofol infusion was increased to 2.5 mg kg^{-1} h^{-1} and if sedation remained insufficient 15 min after the first adjustment, the propofol infusion was increased to 3.0 mg kg^{-1} h^{-1} and likewise increased, if necessary, every 15 min. To facilitate procedures such as washing, punctures, etc., additional boli of propofol (20–50 mg) were permitted. When sedation was excessive (Ramsay score 6), the infusion of propofol was decreased by 0.5 mg kg^{-1} h^{-1} and, if necessary, 15 min later, again by 0.5 mg kg^{-1} h^{-1}. Afterwards the dose of the analgesic was reduced by 2.5 μg kg^{-1} h^{-1} for remifentanil and by 0.25 μg kg^{-1} h^{-1} for sufentanil, respectively.

In case of insufficient analgesia, the dose of the opioid was doubled (remifentanil 10 μg kg^{-1} h^{-1} or sufentanil 1.0 μg kg^{-1} h^{-1}), and if the pain remained 15 min after the first adjustment, the dose was increased to remifentanil 15 μg kg^{-1} h^{-1} or sufentanil 1.5 μg kg^{-1} h^{-1}, and likewise increased, if necessary, every 15 min.

The degree of sedation and the pain score was assessed every 2 h and the dose of propofol and/or the opioid was adjusted accordingly. In case of inadequate sedation (Ramsay score <2), or spontaneous complaint of pain between scheduled observation intervals, drug doses were adjusted as described.

Patients were ventilated to normocapnia (mandatory minute ventilation by respirator EVITA 2–4, Draeger Werke AG, Lübeck, Germany).

Measurements

The continuous analgesic and sedative medication was temporarily stopped after 24 h. Immediately before and 10 and 30 min after the following parameters were determined: systolic (SAP) and diastolic (DAP) invasive arterial pressure, heart rate, arterial carbon dioxide, oxygen and pH, spontaneous ventilation as a percentage of respiratory minute volume, degree of sedation, and pain score. Drug administration was recommenced after the 30 min measurement or immediately (together with a bolus of propofol) if the patient complained of pain or had a Ramsay score of <2.

The values for the sedation score and fraction of spontaneous ventilation are expressed as median (25th, 75th percentile), values for the pain score are expressed as frequencies. The data for arterial pressure, heart rate, pH, arterial carbon dioxide and oxygen are reported as their mean (SD). The Wilcoxon signed-ranks test was used to determine the effect of remifentanil (0, 10 min) and Friedman test followed by Dunn's method was conducted to determine the effect of sufentanil (0, 10, 30 min) on HR, SAP, DAP, pH, Pa_{CO_2}, degree of sedation, pain score and fraction of spontaneous ventilation. The Mann–Whitney *U*-test was used to evaluate differences between groups (0, 10 min). Statistical analysis was performed with the software package Sigma Stat for Windows Version 2.03 (SPSS Inc., USA). $P<0.05$ was considered significant for all tests.

Results

Of the 21 patients recruited, 20 completed the study. One patient underwent emergency surgery during the measurements (patient no. 14; sufentanil) and was excluded from the study. There were no statistically significant differences in patient characteristics between the groups (Table 1). There was no significant difference with respect to midazolam or fentanyl dose before the start of the trial (remifentanil group: fentanyl 0.21 (0.32) mg h^{-1}, midazolam 3.76 (2.97)

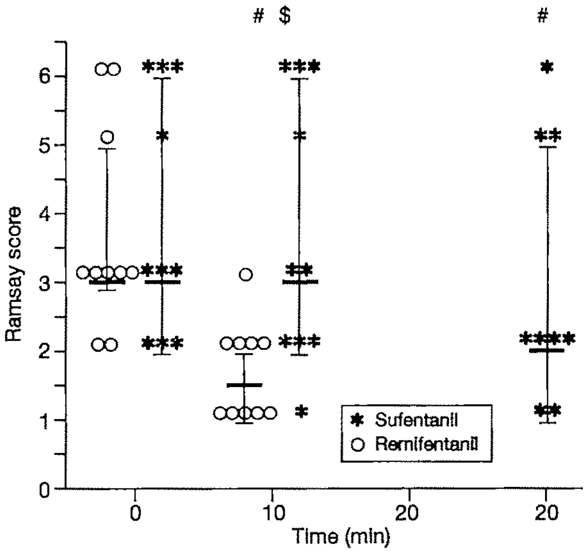

Fig 1 Ramsay score[9] after terminating a continuous infusion of either remifentanil/propofol or sufentanil/propofol over a period of 24 h. Data are expressed as median (black horizontal bar with 25th/75th percentile) and absolute values. $P<0.05 for remifentanil *vs* sufentanil; #$P<0.05$ for remifentanil or sufentanil *vs* baseline value. Ramsay score: (1) anxious and agitated or restless or both; (2) cooperative, orientated, tranquil; (3) patient responds to commands only; (4) brisk response to a light glabellar tap or loud auditory stimulus; (5) sluggish response to light glabellar tap or loud auditory stimulus; (6) no response. No data exist for the remifentanil group 30 min after terminating the continuous administration because nine patients in the remifentanil group woke up within 10–20 min. Thus, the measurements had to be stopped and the continuous administration to be restarted before the end of the scheduled 30 min evaluation interval.

Table 2 Number of patients complaining of pain after terminating a remifentanil/propofol or sufentanil/propofol infusion. Data are expressed as frequencies. *$P=0.014$ for remifentanil (10 min) *vs* sufentanil (10 min). No complete data exist for the remifentanil group and the sufentanil group 30 min after terminating the continuous administration because nine patients in the remifentanil group and one patient in the sufentanil recovered within 10–20 min

		0 min	10 min	30 min
Remifentanil	Patients complaining of pain	1	6*	1
	Patients denying pain	6	3*	
	No reaction because of sedation (Ramsay score >3)	3	1*	
	Number of patients not requiring restart of infusion	10	10	1
Sufentanil	Patients complaining of pain	0	0*	1
	Patients negating pain	6	6*	5
	No reaction because of sedation (Ramsay score >3)	4	4*	3
	Number of patients not requiring restart of infusion	10	10	9

Table 3 Haemodynamic parameters after terminating a continuous infusion of either remifentanil/propofol or sufentanil/propofol over a period of 24 h. Data are expressed as mean (SD). *$P<0.05$ for remifentanil (10 min) *vs* sufentanil (10 min), †$P<0.05$ for remifentanil (0 min) *vs* remifentanil (10 min), ‡$P<0.05$ for sufentanil (0 min) *vs* sufentanil (30 min). No data exist for the remifentanil group 30 min after terminating the continuous administration because the patients in the remifentanil group woke up within 10–20 min. Thus, the measurements had to be stopped and the continuous administration to be restarted before the end of the scheduled 30 min evaluation interval

Systolic/diastolic pressure (mm Hg)	0 min	10 min	30 min
Remifentanil	132 (20)†/58 (9)†	160 (30)*†/75 (19)*†	
Sufentanil	122 (17)‡/62 (10)‡	120 (16)*/60 (4)*	149 (34)‡/70 (11)‡
Heart rate (beats min^{-1})			
Remifentanil	69 (13.0)†	78 (13.9)†	
Sufentanil	79 (27.3)‡	83 (26.8)	90 (25.0)‡

mg h^{-1}; sufentanil group: fentanyl 0.13 (0.08) mg h^{-1}, midazolam 2.73 (1.71) mg h^{-1}) (Table 1).

To achieve adequate analgesia and sedation, patients in the remifentanil group required mean doses of remifentanil 10.6 μg kg^{-1} h^{-1} and propofol 2.1 mg kg^{-1} h^{-1} and, in the sufentanil group, sufentanil 0.5 μg kg^{-1} h^{-1} and propofol 1.3 mg kg^{-1} h^{-1}. The propofol dose was significantly higher in the remifentanil group ($P=0.012$).

Immediately before terminating the continuous infusion, there was no difference between groups with respect to the degree of sedation as indicated by the Ramsay score (median: 3 in both groups, Fig. 1). During the first 10 min after stopping the administration of the infusions, in the sufentanil group the Ramsay score (median) remained unchanged (3) compared with the control and decreased significantly (2, $P<0.05$), 30 min after terminating the infusion. In the remifentanil group the Ramsay score significantly ($P=0.002$) decreased from 3 (control) to 1.5, 10 min after stopping the analgesic and sedative infusion. The difference between groups at the 10-min time point was significant ($P=0.015$ for remifentanil versus sufentanil, Fig. 1). During the following 20 min of the scheduled observation period, nine patients in the remifentanil group emerged from analgesia and sedation (Ramsay score <2) and measurements were stopped and infusion was recommenced. Subsequently, valid data are available only for one patient in the remifentanil group at 30 min. In the sufentanil group, the continuous infusion had to be restarted only once before completing the 30 min evaluation interval.

With respect to the pain scores, no significant differences between the investigated groups immediately before stopping the infusion were seen. Ten minutes after terminating the infusion, six patients in the remifentanil group complained of pain, three patients denied pain and one patient did not react because of deep sedation; in the sufentanil group all patients negated pain ($n=6$) or did not react because of deep sedation ($n=4$) ($P=0.055$ for remifentanil 0 min versus remifentanil 10 min; $P=0.014$ for remifentanil 10 min *vs* sufentanil 10 min; Table 2). In the sufentanil group the first pain complaint was observed after 30 min (one patient; Table 2).

Arterial pH- and Pa_{CO_2}-values did not differ significantly between the groups during the investigation period (remifentanil: control pH 7.47 (0.06), Pa_{CO_2} 5.15 (1.0) kPa; 10 min pH 7.46 (0.06), Pa_{CO_2} 5.16 (1.10) kPa; sufentanil: control pH 7.45 (0.04), Pa_{CO_2} 5.17 (0.82) kPa; 10 min pH 7.45 (0.04), Pa_{CO_2} 5.05 (0.79) kPa; 30 min pH 7.45 (0.03), Pa_{CO_2} 5.04 (0.81) kPa). After 24 h of continuous analgesic and sedative infusion, the incidence of spontaneous ventilation in the remifentanil group increased from 23 to 56% within the first 10 min after terminating the infusion. In the sufentanil group the incidence remained unchanged (22%) during the first 10 min and increased to 53% 30 min after terminating the infusion (not significant).

Mean systolic and diastolic invasive arterial pressure significantly increased in the remifentanil group 10 min after terminating infusion compared with baseline values (SAP P=0.002, DAP P=0.002) and were significantly elevated compared with the values obtained in the sufentanil group (SAP P=0.002, DAP: P=0.013). In the sufentanil group, mean systolic and diastolic arterial pressure increased significantly 30 min after discontinuing the infusion (SAP: P<0.05; DAP: P<0.05, values shown in Table 3). No significant changes in heart rates were observed in or between groups.

Discussion

In our investigation we studied the feasibility of providing analgesia and sedation for ICU patients with continuous administration of either propofol/remifentanil or propofol/sufentanil and the time to neurological recovery after discontinuing the analgesic and sedative medication. We chose a 24 h period of study to be sure that any effects of sedative or analgesic drugs used before the start of our investigation would no longer be of significance.

We were aware of the difficulty of separating sedation and analgesia in an intubated and deeply sedated patient. Another major problem of our study was differentiating between the effects of propofol and the opioids, as both drugs possess sedative qualities and act synergistically. Using a fixed dose of propofol, the comparison between groups would have been possible under standardized conditions. However, with administration of a fixed high propofol dose, sufficient for all patients, the dose of the opioid would have to be reduced to such a degree that emergence from analgesia-sedation would mainly reflect emergence from propofol sedation and differences between the duration of effect of the opioids would have been concealed. On the other hand, some patients clearly had no pain during the study, but were anxious and agitated (Ramsay 1). Increasing the dose of the analgesic would not have changed this state. These patients would have suffered discomfort without a deeper degree of sedation. Therefore, the study design had to permit an increase of the dose of propofol because of ethical considerations.

Remifentanil has previously been proven to be effective in postoperative pain management after abdominal, spine and thoracic surgery or joint replacement using a mean dose of 6 μg kg^{-1} h^{-1}.[10] It is well known that the amount of analgesics required by ICU patients is lower than the dose necessary to provide analgesia during surgery. Nevertheless, the initial dose of 5 μg kg^{-1} h^{-1} in our study was not sufficient and had to be increased in most of the patients. The mean remifentanil dose finally required by our patients (10.6 μg kg^{-1} h^{-1}) has been reported to provide adequate analgesia during several surgical procedures.[11]

By contrast, compared with data published by other authors, the mean sufentanil dose required by the patients in our study (0.5 μg kg^{-1} h^{-1}) was rather low.[5 8] Wappler and colleagues[8] used 0.4–1.5 μg kg^{-1} h^{-1} sufentanil in combination with midazolam for analgesia and sedation of mechanically ventilated ICU patients and Hofbauer and colleagues[5] administered 0.75–1.0 μg kg^{-1} h^{-1} sufentanil combined with midazolam in ICU patients requiring mechanical ventilation for more than 96 h. Nevertheless, the scheduled initial dose in the present study proved sufficient. In addition, in many cases the supplementary dose of 2 mg kg^{-1} h^{-1} propofol initially set in our study could even be reduced. Once adjusted by clinical assessment of pain, neither the dose of remifentanil or sufentanil had to be reduced in any of the patients during the 24 h observation period. This pattern suggests that neither remifentanil or sufentanil accumulated after a 24 h infusion period, although it has been demonstrated for sufentanil, that the context-sensitive half time increases continuously after 25 min of continuous infusion.[3 12 13] By contrast, Egan and colleagues[3] determined the context-sensitive half time for remifentanil to be 3–4 min, independent of the duration of infusion.

Patients in the remifentanil group required significantly more propofol than patients in the sufentanil group. Therefore, it may be that the analgesic dosages used in our study were not equivalent and differences in the pharmacodynamic effects of remifentanil and sufentanil may be responsible for the different propofol requirements. Sufentanil has a greater hypnotic potency than other opiates, for example, morphine, fentanyl, alfentanil or remifentanil, and has been proven to be suitable as monoanaesthetic for analgesia and sedation in ICU patients.[7 8 14–16] As no patient complained of pain during continuous infusion of remifentanil, the higher dosage of propofol needed in this group is most probably a result of a less pronounced hypnotic potency of remifentanil, rather than an insufficient analgesic effect provided by the chosen dose of remifentanil. However, there surely exists a drug interaction between propofol and both opioids. So one must be aware of the difficulty of separating the clinical effects of analgesia and sedation at such high levels of drug effect.

We observed pronounced differences between the groups with respect to time required for recovery. We assume that, even at the 10-min time point, a substantial sedative effect of propofol no longer existed in any patient because, in the remifentanil group, no sedative effect of propofol was present 10 min after terminating the infusion in spite of the higher propofol dose in this group. Therefore, we attribute the poorer recovery in the sufentanil group to the sedative effect of sufentanil.

In most patients on the ICU it would not be of particular advantage to decrease the emergence from analgesia and sedation to a few minutes. Thus, the use of an expensive analgesic drug like remifentanil may still remain the exception rather than the rule in the future. It might even be more comfortable for the patient to be treated with longer acting opioids as analgesia does not fade immediately after stopping their administration. This might be one of the reasons why morphine and fentanyl were recommended as the preferred analgesic agents for the critically ill by a consensus conference of 40 experts in 1995.[4]

However, there are situations requiring regular neurological assessment by clinical signs and remifentamil may be advantageous in these cases.[17]

In conclusion, the use of remifentanil combined with propofol up to 24 h postoperation provides adequate analgesia in patients with no intracranial pathology, after elective maxillo-facial surgery or severe trauma. A more rapid emergence from analgesia and sedation with remifentanil compared with sufentanil is indicative of the pharmacokinetic properties of remifentanil. Despite high cost and rapid termination of effect, the use of remifentanil may be particularly advantageous in patients suffering from severe intracranial disease or head trauma because it allows intermittent and rapid neurological assessment by clinical examination.

References

1 Nayman J. Measurement and control of postoperative pain. *Ann R Coll Surg Engl* 1979; **61**: 419–26

2 Bonica JJ. Current status of postoperative pain therapy. In: Yokata T, Dubner R, eds. *Current Topics in Pain Research and Therapy*. Amsterdam: Exerpta Medica, 1983; 169

3 Egan TD, Lemmens HJM, Fiset P, *et al.* The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. *Anesthesiology* 1993; **79**: 881–92

4 Shapiro BA, Warren J, Egol AB, *et al.* Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; **23**: 1596–1600

5 Hofbauer R, Tesinsky P, Hammerschmidt V, *et al.* No reduction in the sufentanil requirement of elderly patients undergoing ventilatory support in the medical intensive care unit. *Eur J Anaesthesiol* 1999; **16**: 702–7

6 Kremer MJ, Bachenberg KL. Sedation by infusion: a clinical trial in cardiac surgery patients. *AANA J* 1993; **61**: 273–6

7 Kroll W, List WF. Is sufentanil suitable for long-term sedation of a critically ill patient? *Anaesthesist* 1992; **41**: 271–5

8 Wappler F, Scholz J, Prause A, *et al.* Level concept of analgesic dosing in intensive care medicine with sufentanil. *Anästhesiol Intensivmed Notfallmed Schmerzther* 1998; **33**: 8–26

9 Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadalone. *BMJ* 1974; **2**: 656–9

10 Bowdle TA, Camporesi EM, Maysick L, *et al.* A multicenter evaluation of remifentanil for early postoperative analgesia. *Anesth Analg* 1996; **83**: 1292–7

11 Wilhelm W, Biedler A, Larsen R. Remifentanil. Early clinical experiences with 3100 patients. *Anaesthesist* 1997; **46**: 992–7

12 Egan TD. Remifentanil pharmacokinetics and pharmacodynamics—a preliminary appraisal. *Clin Pharmacokinet* 1995; **29**: 80–94

13 Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–41

14 Coda BA, O'Sullivan B, Donaldson G, *et al.* Comparative efficacy of patient-controlled administration of morphine, hydromorphone or sufentanil for the treatment of oral mucositis pain following bone marrow transplantation. *Pain* 1997; **72**: 333–46

15 Ellmauer S. Sufentanil. An alternative to fentanyl/alfentanil? *Anaesthesist* 1994; **43**: 143–58

16 Rathgeber J, Burchardi H. Analgo-sedation during mechanical ventilation—new concepts for new ventilatory modes? *Intensivmed* 1996; **33**: 227–34

17 Warner DS, Hindman BJ, Todd MM, *et al.* Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg* 1996; **83**: 348–53

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Monitoring level of sedation with bispectral EEG analysis: comparison between hypothermic and normothermic cardiopulmonary bypass[†]

D. Schmidlin[1]*, P. Hager[2] and E. R. Schmid[1]

[1]Division of Cardiovascular Anaesthesia, [2]Institute of Anaesthesiology, University Hospital, CH-8091 Zurich, Switzerland

**Corresponding author*

The level of sedation of 28 patients undergoing elective coronary artery bypass grafting with fentanyl–propofol anaesthesia was monitored with bispectral analysis (BIS), spectral edge frequency, and band power of the electroencephalogram. Fourteen patients underwent hypothermic cardiopulmonary bypass (CPB) (32°C, group H), and 14 normothermic CPB (group N). The level of sedation was measured with Observer's Assessment of Alertness/Sedation Score and with Ramsay Sedation Score. BIS was the only EEG measurement that paralleled the clinical course of the patients' sedation level. Values (median, 95% confidence intervals (CI)) changed significantly over time in both groups ($P<0.0001$). In group H, BIS decreased from 97 (95, 99) the day before surgery to 48 (44, 52) after tracheal intubation, to 46 (41, 52) before going off CPB, to 91 (85, 97) immediately before extubation. In group N, values were 93 (91, 97) the day before surgery, 53 (47, 59) after tracheal intubation, 48 (43, 53) before going off CPB, and 90 (84, 96) before extubation. During CPB, BIS values were significantly different between the two groups. Group H had a median of 41 (95% CI, 39, 42), and group N had a median of 49 (95% CI, 48, 51, $P<0.0001$). Peak values of all other processed EEG parameters during anaesthesia and surgery overlapped with values from the day before, when patients had no sedating medication, and these values did not correlate to the patients' course of sedation during the study. There was no explicit recall of the surgery in either group. During the phases of anaesthesia and surgery without CPB, the progression of BIS levels was comparable with previously published data for non-cardiac surgery. During normothermic CPB, the highest BIS values were close to values representing insufficient depth of sedation. It remains to be elucidated whether the much lower BIS values in the hypothermic group were solely a result of brain cooling or if increased serum propofol concentrations, because of slowed pharmacodynamics during hypothermia, also contributed.

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Anaesthesia during cardiopulmonary bypass (CPB) is unique, and potential awareness remains a particular problem.[1–3] The fact that CPB alters pharmacokinetics and pharmacodynamics of drugs and that virtually all physiological processes of drug absorption, distribution, metabolism, and elimination are affected by abnormal conditions, including haemodilution, hypotension, hypothermia, and nonpulsatile blood flow, may lead to administration of inappropriately high or low doses of hypnotics and anaesthetics. The oxygenator and tubing may bind large amounts of drugs used in cardiac anaesthesia.[4 5] Hypothermia and hypothermic CPB are associated with a decreased level of consciousness and decreased metabolic rate. It is, therefore, hypothesized that the high-risk periods occur when the patient is rewarmed.[1]

Many reports suggest that electroencephalographic (EEG) variables do not predict depth of anaesthesia,[6–9]

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but these studies use the classic definition of anaesthetic depth, which means that they do not separate clinical signs, such as the patient's movements or arterial pressure rise, from awareness. The definition of awareness is a degree of consciousness occurring during the period in which the patient is presumed to be under general anaesthesia.[2] This state of consciousness has been revealed post-operatively by testing explicit memory and relies on the patient's ability to remember, with or without prompting, events that occurred during general anaesthesia.[2]

Several years ago, an EEG processing method based on the interfrequency relationship was introduced to clinical monitoring. This bispectral analysis of the EEG has provided a new variable, the bispectral index (BIS), which has been shown to be of great value in detecting consciousness and predicting movement during anaesthesia of surgical patients.[10 11] The EEG and BIS are known not to be affected by transition to CPB,[11] but at the same time there are no studies that compare the effects of moderately hypothermic CPB with those of normothermic CPB for cardiac surgical patients.

The aim of this study was to compare the effects of hypothermic and normothermic CPB on processed EEG parameters and BIS in patients undergoing elective cardiac surgery with a standard anaesthetic procedure. It was thought that phases of undersedation during rewarming or during any phase of normothermic CPB might be detected. The known correlation (or lack of it) between these parameters and the clinical level of sedation during induction of and emergence from anaesthesia in non-cardiac surgery[10] was expected to be reproducible and not different between the two groups.

Patients and methods

After obtaining approval from the ethics committee and written, informed patient consent, 28 patients scheduled for coronary artery bypass grafting (CABG) surgery were enrolled in the study. Fourteen patients underwent hypothermic CPB (group H) and 14 with normothermic CPB (group N). Exclusion criteria were pre-operative neurological disease, severely impaired renal or hepatic function, and a history of alcohol or drug abuse.

Pre-operative medications were continued until the day of surgery, with the exception of acetylsalicylic acid, diuretics, and angiotensin-converting enzyme inhibitors. During the pre-operative visit, the anaesthetist completed pre-operative risk score forms (Euroscore, Parsonnet Score). All patients were premedicated with oral flunitrazepam 45 min before induction.

Routine monitoring included two-channel electrocardiogram (II and V5), radial artery pressure, pulse oximetry, central venous pressure, transoesophageal echocardiography, blood and rectal temperature, capnography, and continuous monitoring of end-expiratory isoflurane concentration. The data from the routine monitoring were logged by computer at 60-s intervals.

Anaesthesia, provided by an anaesthetist blinded for EEG data, was induced with i.v. flunitrazepam and fentanyl. At loss of consciousness, the patients were paralysed with pancuronium, 0.1 mg kg^{-1}, the trachea was intubated, and the lungs were ventilated with air/oxygen by a Servo 900C ventilator (Siemens Elema AB, Upplands Väsby, Sweden). Central venous and, if indicated, pulmonary artery catheters (Baxter Intellicath or VIP, 7.5 F, Baxter Healthcare Corp., Irvine, CA, USA) were placed via the right internal jugular vein. Anaesthesia before CPB consisted of additional fentanyl and was supplemented, if indicated, with isoflurane. Inadequate anaesthesia was defined as an increase in mean arterial pressure of $\geq$15% above the normal arterial pressure for that patient (the mean of three pre-operative measurements) or by other autonomic signs, such as sweating or flushing, or somatic responses such as muscle movement, swallowing, or eye movement; and by a Ramsay Sedation Score of <6, which was assessed every 15 min during anaesthesia.[12] During CPB, sedation was provided by propofol, and analgesia was maintained with additional fentanyl.

After surgery, patients remained sedated with propofol in the intensive care unit (ICU) until they had rewarmed completely and had no significant bleeding. Subsequently, they were weaned from mechanical ventilation.

A post-operative risk assessment using APACHE II and SAPS II scoring systems was performed by the ICU residents who were blinded for all intra-operative EEG and BIS data.

We recorded two bipolar EEG channels (FpZ-F7, FpZ-F8 with an Aspect A 1000 EEG analyzer, Aspect Medical Systems, Natick, MA, USA) as recommended for BIS monitoring by the manufacturer of the monitor. Zipprep electrodes (Aspect Medical Systems) were applied to the scalp after mild abrasion with a cotton sponge, resulting in contact impedance <5 kΩ.

A baseline BIS value was recorded the day before surgery to avoid the effect of premedication. Recordings were made before induction, after induction, immediately before and after laryngoscopy and tracheal intubation, immediately before CPB, at 15-min intervals during CPB, immediately after CPB, at the end of surgery, and in the ICU when patients began to move.

The raw EEG signals were band-pass filtered to 0.5–30 Hz and processed in real time using version 3.12 of the BIS algorithm. Additional quantitative EEG variables, including absolute band powers and 95th-percentile spectral edge frequency, were also calculated online. With the help of the serial port, the quantitative EEG variables were digitally recorded every 5 s for the duration of the study, as were time-synchronized markers describing all clinical assessment events. Data were stored on a personal computer as text file and analysed off line with the help of Microsoft Excel™ (Microsoft Corp., Redmond, WA, USA).

Parameters containing BIS values above 100, parameters showing sudden high values in the electromyogram, as well as electrocautery, were identified as artefacts and were eliminated from further analysis. A band-power determination for the range 70–110 Hz was performed before band-pass filtering. The mean of the two EEG channels was used for statistical analysis. The values of EEG parameters at each event were calculated by averaging the values during 60–360 s of stable recording immediately before and after the selected events.

The level of sedation following premedication and before induction of anaesthesia was assessed by using the Observer's Assessment of Alertness/Sedation Score (OAAS)[13] (1=no response to tactile stimulation, 5=wide awake).

All patients were interviewed at 18 h after extubation by an investigator (P.H.). After an initial introduction, the structured interview began. Each patient was asked the following standard set of questions:

(1) What was the last thing you remember before surgery?

(2) What was the very next thing you remember?

(3) Can you remember anything in between these two periods?

(4) Did you have any dreams during your operation?

Data were analysed with ANOVA for repeated measurements and Greenhous-Geisser correction, with Mann–Whitney *U*-test and Bonferroni correction for differences between specific time points. For differences between groups with respect to pre-operative and intra-operative patient and procedure data, factorial ANOVA and Mann–Whitney *U*-test without Bonferroni correction were performed. *P* values of <0.05 were considered significant. Analyses were performed on an Apple Power Mac G 3 computer (MacOS 8.6) with Statview 4.5 and SuperAnova 1.11 software (Abacus Concepts Inc., Berkeley, CA, USA).

Results

Data as median value and 95% CI. Patient groups did not differ with respect to age, sex, body weight, pre-operative risk scores, or pre-operative medication (beta-blockers, nitrates, angiotensin-converting enzyme inhibitors, and calcium antagonists). There was also no difference in the doses of flunitrazepam, fentanyl, propofol, or isoflurane (Table 1).

The number of CABG anastomoses performed and the duration of the procedure did not differ between groups. However, duration of CPB, aortic cross-clamp time, and CPB temperature were significantly different (Table 2).

At the beginning of surgery, there was a significant increase in mean arterial pressure during tracheal intubation (median 71 (95% CI, 67, 75) before *vs* 77 (71, 83) after intubation) and during sternal split (76 (72, 80) before *vs* 84 (80, 88) after sternal split). Heart rate also significantly increased after sternal split (56 (52, 60) before *vs* 59 (57, 63) after). The two groups did not differ significantly with respect to mean arterial pressure or heart rate during the study period.

BIS values changed significantly over time (Fig. 1); baseline values were as expected for alert patients the day before surgery: median 97 (95% CI 95, 99) (group H) and 93 (91, 97) (group N). BIS values were lower when premedicated patients arrived in the operating theatre: 80 (76, 84) (group H) and 89 (77, 101) (group N). Values decreased further after induction of anaesthesia: 48 (44, 52) (group H) and 53 (47, 59) (group N). After discontinuation of sedation, BIS values gradually increased until they reached pre-operative baseline values before extubation in the ICU: 91 (85, 97) (group H) and 90 (84, 96) (group N). These values were not significantly different between groups (Fig. 1).

During CPB, BIS values were significantly lower in group H than in group N: median 41 (95% CI, 39, 42) (group H) *vs* 49 (48, 51) (group N) (*P*=0.0001). However, when corrected for temperature, BIS values were not significantly different between groups and did not change significantly over time (Fig. 2).

BIS was the only EEG-derived measurement that represented the time course of the patient's sedation, assessed either by OAAS or by clinical judgement (Ramsay Sedation Score, other autonomic signs). No overlapping occurred between values obtained the day before surgery (when patients were without sedating medication) and values obtained during anaesthesia and surgery (Fig. 1).

The time course of the remaining EEG parameters did not reflect sedation: values were either higher than baseline (as expected for A beta following benzodiazepine premedication) when patients arrived in the operating theatre (SEF, A alpha, A beta, A theta) (Fig. 1) or did not significantly change over time (A delta). Overlapping between values obtained the day before surgery and intra-operative values occurred in all these parameters.

With the exception of A theta, which showed no dependence on CPB temperature (median 50 (95% CI, 49, 50) (group H) *vs* 48 (47, 49) (group N)), during CPB, group H had significantly lower EEG parameter values than group N: SEF, 10 (10, 11) (group H) *vs* 13 (13, 14) (group N) (*P*=0.0016, Fig. 1); A alpha, 48 (47, 49) (group H) *vs* 51 (50, 52) (group N) (*P*=0.0001); A beta, 42 (41, 43) (group H) *vs* 44 (43, 45) (group N) (*P*=0.0001); A delta, 48 (47, 49) (group H) *vs* 51 (50, 52) (group N) (*P*=0.0001).

The values for OAAS differed significantly between those obtained the day before surgery (when all patients were fully alert and had a score of 5) and those obtained after premedication as well as those obtained shortly before induction of anaesthesia (Table 2). One of the patients remembered the insertion of catheters under local anaesthesia. The last thing all the other patients remembered was leaving their room on the ward, and no patients had explicit memory of intra-operative events as stated in the post-

Table 1 Patient and anaesthetic characteristics. Values are expressed as median and 95% confidence interval. No significant differences between groups. Abbreviations: CPB=cardiopulmonary bypass; LV=left ventricular; ACE=angiotensin-converting enzyme; Ca=calcium; EEG=electroencephalogram

	Hypothermic CPB 14 patients	**Normothermic CPB 14 patients**
Age (yr) [range]	66 (62, 70) [range 54–78]	68 (64, 72) [range 49–77]
Sex (f/m)	4/10	2/12
Body Mass Index	26.1 (24.5, 27.8)	26.3 (25.1, 27.5)
Pre-op LV ejection fraction (%)	62.5 (55.5, 69.5)	60.0 (63.4, 66.6)
Euroscore	3 (1, 5)	3 (1, 5)
Parsonnet Score	6 (4, 8)	4 (4, 8)
Pre-operative medication	*Number of patients*	*Number of patients*
Beta-blockers	12	10
Nitrates	5	6
ACE inhibitors	5	2
Ca antagonists	5	3
Premedication		
Flunitrazepam (μg kg^{-1})	24 (22, 26)	26 (23, 29)
Intra-operative anaesthetics		
Flunitrazepam (μg kg^{-1})	24 (20, 28)	19 (17, 21)
Fentanyl (μg kg^{-1})	36 (32, 40)	32 (30, 36)
Propofol during CPB (mg kg^{-1} h^{-1})	2.0 (1.6, 2.4)	1.6 (1.2, 2.0)
Propofol during entire anaesthesia (mg kg^{-1} h^{-1})	1.6 (1.2, 2.0)	1.3 (1.1, 1.5)
Isoflurane (vol. %)	0.14 (0.08, 0.2)	0.13 (0.07, 0.19)
Anaesthesia time (h)	7.0 (6.4, 7.6)	7.2 (6.4, 8.0)

Table 2 Sedation, surgical procedures and outcome. *Significantly different from the other two times (day before, entering the OR, or before induction) ($P<0.0001$). **Significantly different between groups ($P=0.002$). ***Significantly different between groups ($P=0.0003$). ****Significantly different between groups ($P<0.0001$). Values are expressed as median and 95% confidence interval. Abbreviations: CPB=cardiopulmonary bypass; OR=operating room; ICU=intensive care unit; ECG=electrocardiogram; RBB=right bundle branch block

	Hypothermic CPB 14 patients	**Normothermic CPB 14 patients**
Observer's Assessment of Alertness/Sedation Score		
Day before surgery	5 (0)	5 (0)
Entering the OR (premedicated)	3.8 (3.4, 4.2)	3.8 (3.6, 4.0)*
Before induction	3.4 (2.8, 4.0)	3.4 (3.0, 3.8)*
Surgical procedures		
Operation time (h)	4.6 (4.2, 5.0)	4.8 (4.2, 5.0)
CPB duration (min)	136 (118, 153)	87 (74, 100) **
Aortic cross-clamp time (min)	76 (64, 88)	45 (37, 53) ***
CPB temperature (°C)	33.5 (29.9, 34.1)	37.7 (37.5, 37.9) ****
Anastomoses performed	5.0 (4.4, 5.6)	5.0 (4.4, 5.6)
Outcome/complications		
APACHE II	12 (10, 13)	13 (12, 14)
SAPS II	25 (23, 27)	24 (21, 27)
Neurological dysfunction (transient post-op delirium)	2	1
Post-operative intubation time (h)	5.2 (2.7, 6.3)	4.2 (3.6, 4.8)
Length of stay in ICU (days)	2.0 (1.2, 2.8)	1.0 (0.4, 1.6)
ECG changes	0	1 (new RBB)
Atrial fibrillation	3	2
Significant enzyme elevation	0	0

operative structured interview. Patients did not wake up before weaning from the ventilator in the ICU.

The two groups did not differ with respect to the measured outcome variables (Table 2).

Discussion

BIS values found during our study were representative of sedation depth in all phases of anaesthesia without CPB and were comparable with previously published data for non-cardiac surgery. During CPB, there was a significant difference between the hypothermic group (group H) and the normothermic group (group N), and there were values in the normothermic group that were close to the level of undersedation, according to previous studies.

It is now well recognized that each anaesthetic produces a unique spectrum of pharmacologic actions, so the concept of a common 'depth of anaesthesia' may need to be revised to reflect the separate components of the ideal anaesthetic state. In general, a monitor of depth of anaesthesia can

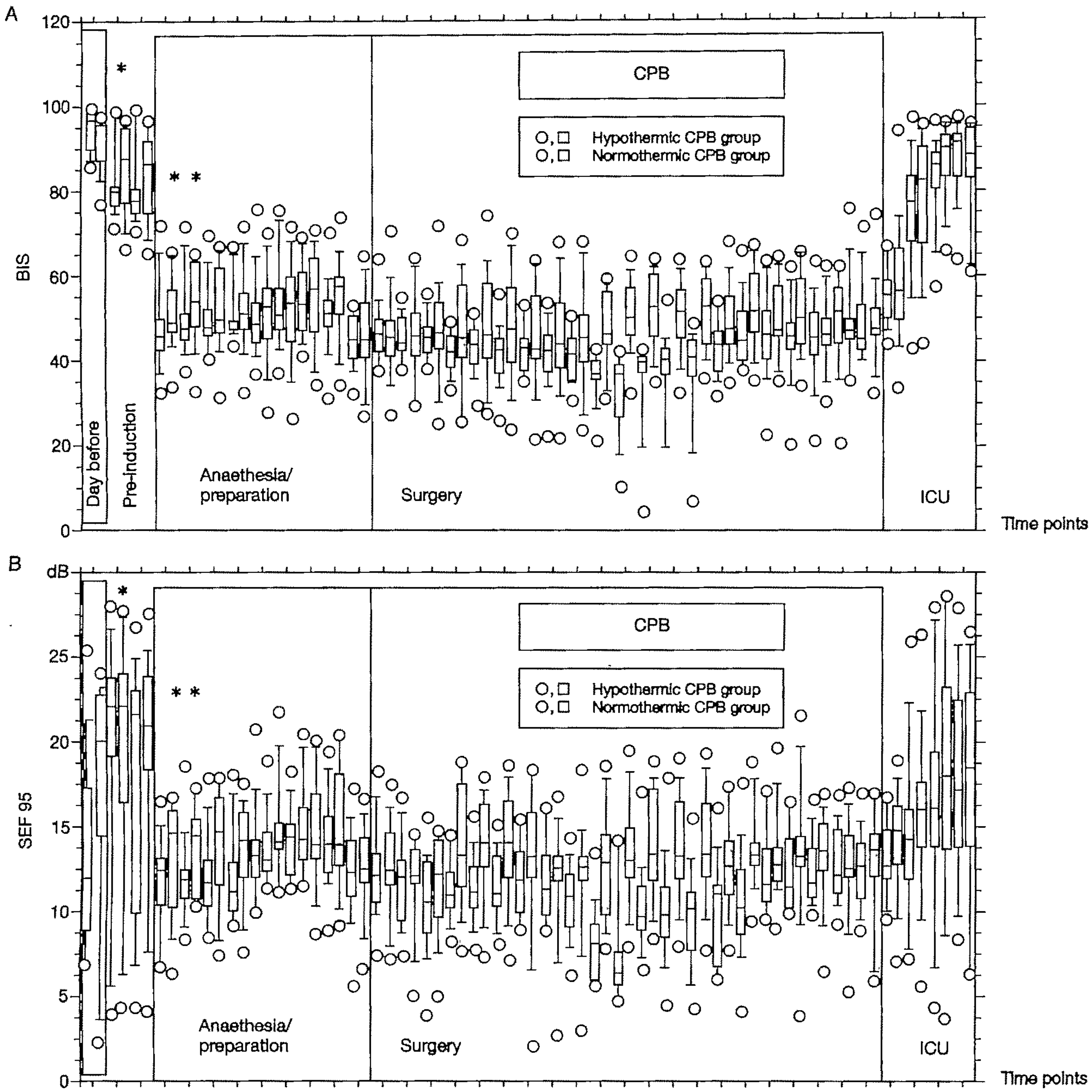

Fig 1 Processed EEG parameters (BIS, SEF 95). Open symbols represent the hypothermic CPB group, hatched symbols the normothermic CPB group. Significant changes over time are indicated by *, **, and ¶, as described below. Values of the box plots are expressed as median, 10th, 25th, 75th, and 90th percentile. Isolated values are depicted as circles. (A) BIS (bispectral analysis). *Day before surgery *vs* before induction of anaesthesia; $P=0.0003$. **Before induction *vs* after induction of anaesthesia; $P<0.0003$. ¶End of surgery *vs* clinical awakening; ($P<0.0003$). (B) SEF 95 (spectral edge frequency at 95% level). *Day before surgery *vs* before induction of anaesthesia; $P=0.049$. **Before induction *vs* after induction of anaesthesia; $P=0.0024$. ¶End of surgery *vs* clinical awakening; $P=0.0018$.

measure only one of these components, such as level of sedation, obtundity of noxious reflexes, or neuromuscular block.[14] Electromyogram signals of the frontotemporal region, however, play a role in the BIS algorithm; BIS values, therefore, may be influenced by temporalis muscle activity. In a study comparing BIS and frontal electromyogram at different propofol concentrations, Struys and colleagues[15] found only a weak correlation between these two parameters, especially during recovery from propofol anaesthesia.[11] Obligatory electrocautery caused interruption of the EEG signal; therefore, some critical phases of the operation were not monitored by that means.

EEG contamination by artefacts may be an issue when patients are at light levels of sedation and when muscle relaxation is no longer present, especially during emergence from anaesthesia in the ICU. Another source of artefacts is

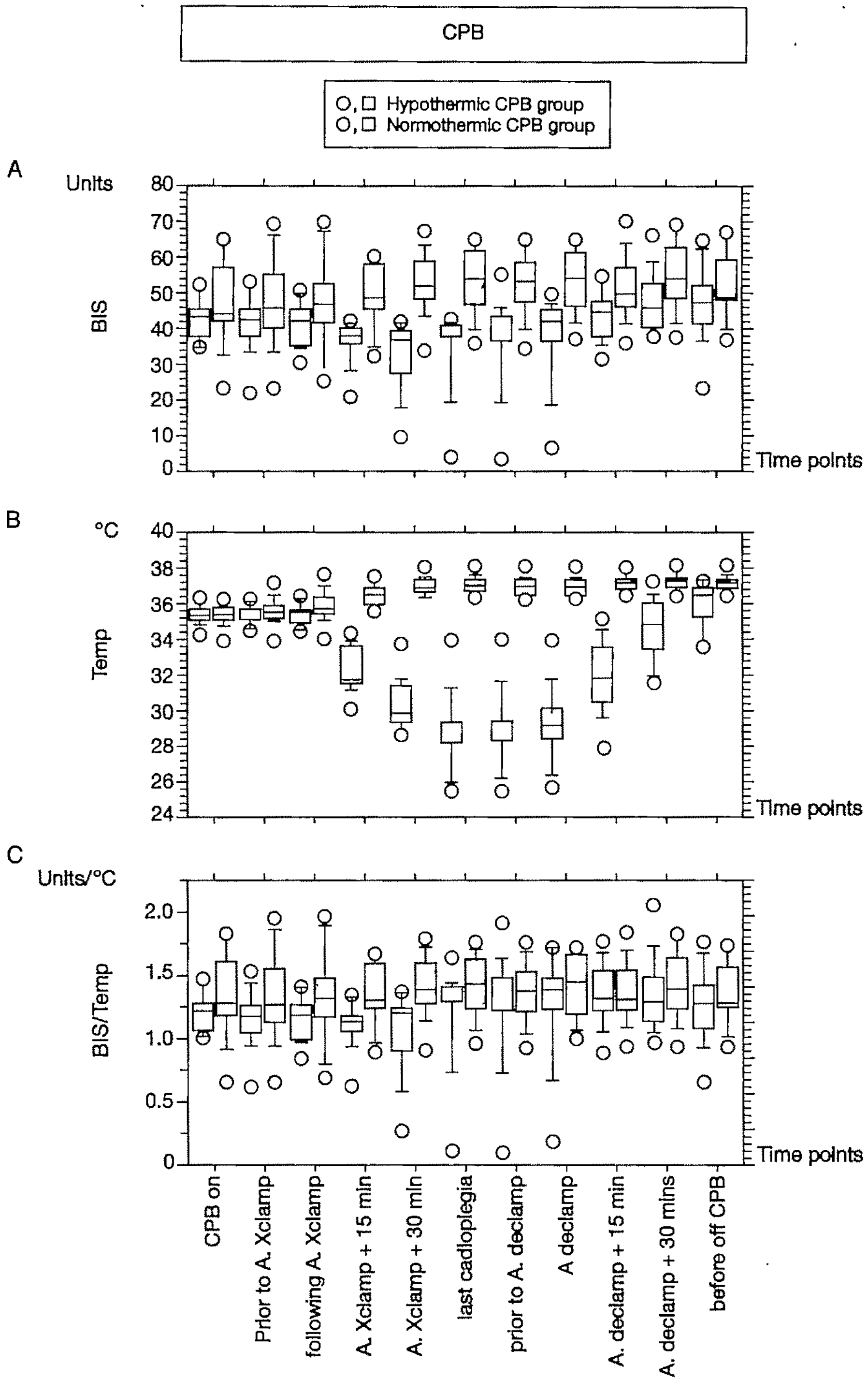

Fig 2 BIS and temperature during CPB. Open symbols represent the hypothermic CPB group, hatched symbols the normothermic CPB group. Values of the box plots are expressed as median, 10th, 25th, 75th, and 90th percentile. Isolated values are depicted as circles. (A) BIS during CPB. Values between groups were significantly different; $P=0.001$. (B) Blood temperature during CPB. Values between groups were significantly different; $P<0.0001$. (C) BIS values divided by blood temperature. There was no difference over time and no difference between the hypothermic and normothermic CPB groups.

direct moving of the EEG cables, which frequently happened because of manipulations of the transoesophageal probe or the pulmonary artery catheter. The electromyogram displayed on the BIS monitor made detection of these artefacts easy.

Because implicit memory recall was not assessed, we cannot exclude the possibility that patients perceived information during surgery that they did not explicitly recall. It is known that patients may respond to commands and display consciousness during surgery without postoperative explicit memory.[16] In addition, flunitrazepam (like other benzodiazepines) produces at least some pharmacologically reversible antegrade amnesia,[17] a fact that may reduce the formation of explicit memory further. Because of its low reported incidence,[1–3] to detect cases of explicit awareness during CPB would require a much larger study population.

Different anaesthesia was used before CPB than during and after the bypass. At our institution, it is neither usual nor feasible to add isoflurane to the CPB circuit. Therefore, propofol was started with aortic cannulation and continued until weaning from the respirator in the ICU. There was no difference between groups, however, in application dose of isoflurane or propofol at any time point.

This study demonstrates that the decrease in OAAS rating (e.g. the decrease in patients' alertness) following flunitrazepam-induced sedation is reflected by BIS (Fig. 1). This finding was described by Liu and co-workers[18] for midazolam. As reported by others,[19 20] we found a benzodiazepine-induced increase in high-frequency beta power with sedation. SEF 95 also increased significantly following premedication, although variation of the values was very large (Fig. 1).

We found two phases of significantly increased mean arterial pressure—after intubation and after sternotomy. BIS levels in the same periods did not increase (Fig. 1). The difference between level of sedation and autonomic reaction to noxious stimuli was evident at these two time points.

BIS is an easily readable monitor of sedation in the phases of anaesthetic induction and emergence from anaesthesia, as demonstrated in non-cardiac surgery.[21 22] Our results for BIS values as well as for the other EEG parameters are in accordance with the findings of those studies.

During emergence from anaesthesia, BIS levels gradually increased until they reached pre-anaesthetic levels immediately before extubation. As has been shown in non-cardiac surgical patients, the increasing BIS values paralleled clinical awakening, individually and in the entire study group. We did not find overlapping BIS values between pre-anaesthetic levels and values during hypothermic CPB, in contrast to Doi and colleagues.[11]

Initiating CPB did not affect BIS levels. The fact that hypothermia significantly decreases BIS levels has been reported previously[11] and is expected because other EEG parameters also decrease when brain temperature decreases. Contrary to Doi's data, we found no variation in BIS values in the hypothermic group (Fig. 1). In his study, however, a different EEG-electrode montage (At1 and At2 with Fpz as reference and Fp1 as ground electrodes), a different propofol drug regimen (target-controlled infusion system) with target values between 3.5 (before CPB) and 2.0 mg ml^{-1} (30 min following CPB) as well as a different opioid (alfentanil) with continuous application technique was used. It remains speculative whether these methodological differences may account for the higher variation of BIS values during hypothermia in Doi's study.

We found no BIS value above 55 during hypothermia. Neither the difference from Doi's data nor the clinical significance of the lower BIS levels during hypothermia can be explained by our findings. We can only speculate that while we used almost identical doses of propofol in both groups during CPB, a relative underdosing of propofol during normothermia, as expressed by relatively high values of BIS, may have resulted. Plasma concentrations with comparable doses of propofol during hypothermic CPB were shown to be within the therapeutic range.[23 24] In the normothermic group, the 90th percentile of BIS during CPB was 64, whereas it was 54 in the hypothermic group. This means that some normothermic CPB patients (Fig. 2) exhibited critically high levels of BIS during extracorporeal circulation. As is known from previous work, BIS95 (the BIS level at which 95% of all patients do not present consciousness or recall) in a combined anaesthesia/sedation with opioids/propofol is about 50 for consciousness and 64 for recall in healthy volunteers.[14 25 26] In patients with midazolam/fentanyl anaesthesia, BIS levels during moderately hypothermic CPB varied considerably, leading to the authors' conclusion that in this type of anaesthesia, BIS does not accurately reflect either serum drug concentrations or the danger of awareness.[27]

The significantly lower BIS values during hypothermic CPB may imply that patients in this group were more sedated than those in the normothermic group, even if there was no measurable difference in sedation level between the groups with our study design. This could be the result of increased propofol blood concentrations due to decreased propofol biotransformation during hypothermia[23] and/or a simple effect of brain cooling and reduced electric activity of the brain. While the median difference of BIS between normothermia and hypothermia was as small as 8 and may seem to be clinically irrelevant, the variation of the values resulted in a considerable number of patients reaching critically high levels in the normothermic group.

It is evident, however, that either a higher dose of propofol for normothermic patients or a lower dose for hypothermic patients is required to achieve the same target BIS values. A controlled infusion of propofol with a target value of BIS must, therefore, be effective independent of temperature, as our data suggest when BIS is normalized for temperature.

To our knowledge, this study is the first to compare sedation by means of processed EEG parameters between patients undergoing hypothermic CPB with those undergoing normothermic CPB for CABG surgery. BIS was the only EEG parameter that correctly paralleled the various states of sedation and anaesthesia, from baseline to sedation and return to consciousness. The remaining EEG parameters measured in our study did not reliably reflect sedation, as reported previously.[15 28]

References

1 Phillips AA, McLean RF, Devitt JH, Harrington EM. Recall of intraoperative events after general anaesthesia and cardiopulmonary bypass. *Can J Anesth* 1993; **40**: 922–6

2 Dowd NP, Cheng DC, Karski JM, Wong DT, Munro JAC, Sandler AN. Intraoperative awareness in fast track cardiac anesthesia. *Anesthesiology* 1998; **89**: 1068–73

3 Tempe DK, Siddiquie RA. Awareness during cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; **13**: 214–9

4 Koren G, Crean P, Klein J, Goresky G, Villamater J, MacLeod SM. Sequestration of fentanyl by the cardiopulmonary bypass (CPBP). *Eur J Clin Pharmacol* 1984; **27**: 51–6

5 Skacel M, Knott C, Reynolds R, Aps C. Extracorporeal circuit sequestration of fentanyl and alfentanil. *Br J Anaesth* 1986; **58**: 947–9

6 White PF, Boyle WA. Relationship between hemodynamic and electroencephalographic changes during general anesthesia. *Anesth Analg* 1989; **68**: 177–81

7 Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power and dominance shift in the determination of depth of anaesthesia. *Acta Anaesthesiol Scand* 1991; **35**: 693–99

8 Dwyer RC, Rampil IJ, Eger EI, Bennett HL. The electroencephalogram does not predict depth of isoflurane anesthesia. *Anesthesiology* 1994; **81**: 403–9

9 Schwender D, Daunderer M, Mulzer S, Klasing S, Finsterer U, Peter K. Spectral edge frequency of the electroencephalogram to monitor 'depth' of anaesthesia with isoflurane or propofol. *Br J Anaesth* 1996; **77**: 179–84

10 Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997; **84**: 185–9

11 Doi M, Gajraj RJ, Mantzaridis H, Kenny GNC. Effects of cardiopulmonary bypass and hypothermia on electroencephalographic variables. *Anaesthesia* 1997; **52**: 1048–55

12 Wahr JA, Plunkett JJ, Ramsay JG, *et al.* Cardiovascular responses during sedation after coronary revascularization. Incidence of myocardial ischemia and hemodynamic episodes with propofol versus midazolam. Institutions of the McSPI Research Group. *Anesthesiology* 1996; **84**: 1350–60

13 Chernik DA, Gillings D, Laine H, *et al.* Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; **10**: 244–51

14 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

15 Struys M, Versichelen L, Mortier E, *et al.* Comparison of spontaneous frontal EMG, EEG power spectrum and bispectral index to monitor propofol drug effect and emergence. *Acta Anaesthesiol Scand* 1998; **42**: 628–36

16 Nordstrom O, Sandin R. Recall during intermittent propofol anaesthesia. *Br J Anaesth* 1996; **76**: 699–701

17 Schaer H, Baasch K, Achtari R. Antagonism of flunitrazepam and fentanyl by flumazenil, naloxone or nalbuphine. *Anaesthesist* 1990; **39**: 26–32

18 Liu J, Singh H, White PF. Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. *Anesthesiology* 1996; **84**: 64–9

19 Tan X, Uchida S, Matsuura M, Nishihara K, Iguchi Y, Kojima T. Benzodiazepine effects on human sleep EEG spectra. A comparison of triazolam and flunitrazepam. *Life Sci* 1998; **63**: 675–84

20 Zickmann B, Boldt J, Wulf K, Hofmann HC, Thiel A, Hempelmann G. Topographic changes in cerebral electric activity after premedication with flunitrazepam. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1994; **29**: 330–37

21 Kearse LA, Manberg P, Chamoun N, deBros F, Zaslavsky A. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. *Anesthesiology* 1994; **8**: 1365–70

22 Kearse LA, Manberg P, DeBros F, Chamoun N, Sinai V. Bispectral analysis of the electroencephalogram during induction of anesthesia may predict hemodynamic responses to laryngoscopy and intubation. *Electroencephalogr Clin Neurophysiol* 1994; **90**: 194–200

23 Russell GN, Wright EL, Fox MA, Douglas EJ, Cockshott ID. Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. *Anaesthesia* 1989; **44**: 205–8

24 Massey NJ, Sherry KM, Oldroyd S, Peacock JE. Pharmacokinetics of an infusion of propofol during cardiac surgery. *Br J Anaesth* 1990; **65**: 475–79

25 Iselin-Chaves IA, Flaishon R, Sebel PS, *et al.* The effect of the interaction of profol and alfentanil on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998; **87**: 949–55

26 Iselin-Chaves IA, El Moalem HE, Gan TJ, Ginsberg B, Glass PS. Changes in the auditory evoked potentials and the bispectral index following propofol or propofol and alfentanil. *Anesthesiology* 2000; **92**: 1300–10

27 Barr G, Anderson RE, Samuelsson S, Öwall A, Jakobsson JG. Fentanyl and midazolam anaesthesia for coronary bypass surgery: a clinical study of bispectral electroencephalogram analysis, drug concentrations and recall. *Br J Anaesth* 2000; **84**: 749–52

28 Traast HS, Kalkman CJ. Electroencephalographic characteristics of emergence from propofol/sufentanil total intravenous anesthesia. *Anesth Analg* 1995; **81**: 366–71

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Inspiratory timing during anaesthesia: a model of cardioventilatory coupling

D. C. Galletly* and P. D. Larsen

Wellington School of Medicine, PO Box 7343, Wellington, New Zealand
**Corresponding author*

We describe a simple model of cardioventilatory coupling in which a hypothetical inspiratory pacemaker is stimulated by a signal related to cardiac action. At suitable values for the control variables (cardiac signal magnitude, heart rate, inspiratory pacemaker rate and inspiratory rate variability), the model was found to: (1) replicate all clinically described patterns of coupling; (2) predict variations in these described patterns and new patterns which were subsequently found in clinical time series; (3) simulate variations in clinically observed breathing frequency variations associated with each coupling pattern; (4) simulate the clinically observed distribution of coupling patterns between heart rate and breathing frequency; (5) explain the invariability of coupling below a critical heart rate/breathing frequency ratio; and (6) simulate the changes in breathing frequency and transitions between coupling patterns from the heart rate time series of human subjects. Although cardioventilatory coupling causes complex breathing rate irregularities during anaesthesia, these are readily explained by three variables, heart rate, intrinsic breathing frequency, and the strength of their interaction. This simple model, along with clinical observations of cardioventilatory coupling may provide a useful non-invasive method to study the respiratory central pattern generator.

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Cardioventilatory coupling is a temporal coherence of cardiac and respiratory rhythms, present in many mammalian species, and common in humans during sleep and general anaesthesia with spontaneous breathing.[1–4] Experimental data suggest that coupling is a triggering of inspiration in response to an unknown afferent signal related to the heart beat. During a breath triggered by cardiac action, inspiration begins approximately 0.5 s following the preceding ECG R wave.[1] However, from breath to breath, this 'coupling interval', and the entrainment ratio (number of heart beats between consecutive inspirations) may vary according to a small number of distinct 'coupling patterns'. These patterns have been classified numerically as I, II, III, IV and uncoupled.[1 5] Uncoupled time series have an apparent random variation of coupling interval or no apparent temporal relationship between heart beats and inspiratory onset. In recordings made during surgery, coupling patterns are unstable with transitions between patterns being common. Because each coupling pattern is associated with a distinct pattern of breathing frequency irregularity,[5] transitions between coupling patterns are accompanied by corresponding changes in the pattern of breathing. To understand breathing irregularities during anaesthesia we should have a clear understanding of coupling patterns, their generation and the reasons for their instability.

We observed clinically that coupling patterns vary according to the ratio of the heart rate to breathing frequency. However, between subjects, the presence and pattern of coupling may differ despite approximately similar heart/breathing frequency ratios. From these observations, we suggested that patterns and their transitions might be explained by the interaction of three variables; heart rate, intrinsic breathing frequency (the breathing frequency in the absence of coupling) and the strength of interaction between the cardiac afferent signal and a hypothetical brain stem inspiratory pacemaker.[5] In this paper we develop and study a simple model of coupling which incorporates these three variables. The model can replicate all of the clinically observed coupling patterns and their associated ventilatory variability.

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Method

The model

We assume the presence of a spontaneous intrinsic inspiratory pacemaker, the instantaneous state of which can be represented by the function (Φ(I)). This function increases linearly from a basal level immediately following a previous inspiratory onset. When Φ(I) reaches a specific threshold (the inspiratory firing threshold), inspiration is triggered; Φ(I) is then reset to a basal level (Fig. 1). The intrinsic ventilatory period (the interval between consecutive inspiratory onsets) is governed by the Φ(I) slope. The breathing frequency generated by Φ(I) alone we term the *intrinsic* breathing frequency (*fi*).

An afferent signal of cardiovascular origin reaches the brain stem soon after the onset of cardiac systole. With each cardiovascular afferent signal, a burst stimulus (M_{Bc}) transiently augments the Φ(I). Because the interval between R wave and inspiratory onset, during human coupling, is approximately 0.5 s, and allowing for a delay in detecting the actual onset of inspiration, we will assume the R wave of cardiac systole and the onset of the cardiac related signal are separated by a constant interval of 0.4 s. The cardiac signal was empirically set to a square wave burst of duration 0.1 s.

With cardiac related bursts transiently augmenting Φ(I), inspiration will occur if either (a) the intrinsic Φ(I) or (b) the cardiac burst transiently augmented Φ(I) exceeds the inspiratory firing threshold. The slope of the Φ(I) can, therefore, be divided into alternating sections of exposed intrinsic slope and sections which are in the 'shadow' of a cardiac burst (Fig. 1). The relative size of these sections and, therefore, the likelihood of cardiac versus intrinsic triggering, varies according to the slope of Φ(I), HR and the cardiac burst magnitude. Although the intrinsic breathing frequency is constant, given a constant Φ(I) slope, the addition of cardiac bursts causes the ventilatory period to vary if the mechanism of inspiratory triggering changes from one breath to the next. In the presence of coupling therefore, the resulting *observed* ventilatory frequency (*fo*) may differ from the intrinsic frequency (*fi*); it is important to note that *fo* will always be equal to or greater than *fi* as a triggered breath will always occur before the expected time of a non-coupled intrinsic breath.

For simplicity, the cardiac pacemaker activity at the sinus node was regarded as equivalent to Φ(I), with a linear cardiac pacemaker function, Φ(C), rising to a cardiac firing threshold at which cardiac systole is initiated and Φ(C) is reset to a baseline value.

Noise can be expected in any biological system and variability is assumed to occur in burst magnitude, Φ(I) slope and HR. To avoid undue complexity, we incorporated variability into our model by varying the value of Φ(I) using a Gaussian distributed random variation. The standard deviation of this Gaussian distribution we will term the Φ(I) slope variability.

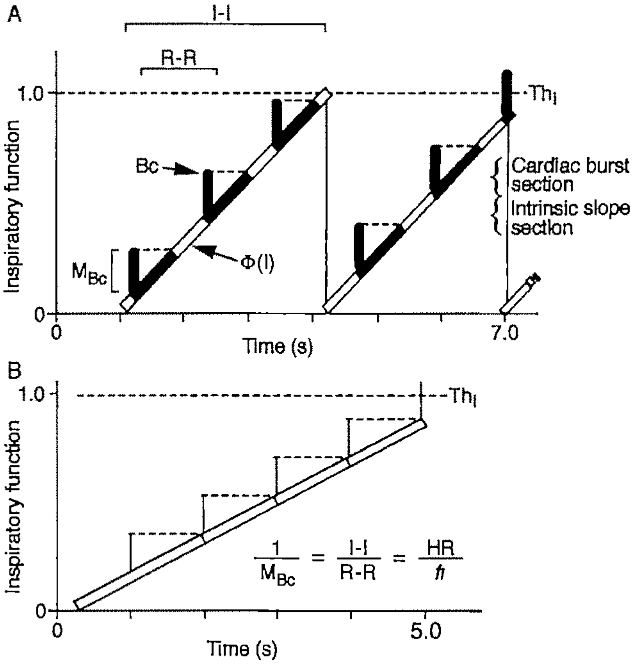

Fig 1 Model features. (A) The inspiratory function Φ(I) increases linearly until, at the inspiratory threshold (Th_I=1.0), inspiration is triggered and Φ(I) is reset to zero. Cardiac related bursts of magnitude M_{Bc} transiently augment Φ(I). The figure shows two inspirations being triggered, the first by the intrinsic pacemaker and the second by a cardiac burst. The Φ(I) slope may be divided into exposed intrinsic sections and cardiac burst sections. (B) There will be a threshold of HR, M_{Bc} and Φ(I) slope beyond which there are no intrinsic sections remaining on Φ(I) and therefore every breath must be initiated by cardiac activity. It can be shown that this critical point occurs when HR/*fi* >1/M_{Bc}, where *fi* is the intrinsic frequency.

Respiratory sinus arrhythmia (RSA) was not examined in any detail in this preliminary description. However in order to determine whether RSA causes major instability in the model we crudely incorporated RSA by transiently reducing cardiac firing threshold following inspiratory onset. In those simulations, which included RSA, we reduced linearly, the cardiac threshold for firing from 1.0, at inspiratory onset to 0.8, 1.5 s following inspiratory onset, returning this firing threshold, linearly, to 1.0 by the following inspiratory onset.

Input variables

The following variables and parameters define the behaviour of the model.

(a) Inspiratory and cardiac firing thresholds; regarded as constant values=1.0.

(b) Φ(I) slope.

(c) Φ(C) slope.

(d) R wave to cardiac burst interval=0.4 s.

(e) Cardiac burst magnitude, M_{Bc}.

(f) Cardiac burst duration=0.1 s.

(g) The magnitude and time course of the cardiac firing threshold lowering by RSA.

(h) Φ(I) slope variability.

Simulation

A computer simulation was written using LabView 5 on a Macintosh PowerBook 1400cs and iterated in time steps of 0.01 s.

Coupling interval (RI) pattern

From simulated time series, we determined the timing of consecutive R waves and inspiratory onsets. Within each breathing cycle (from inspiration to inspiration) we determined the time from each enclosed R wave to the following inspiratory onset. Coupling patterns are observed when these RI intervals are plotted as a time series (the RI plot). Within each breath there will be a number of RI intervals (equal to the entrainment ratio), the shortest of which (RI_1) will generally correspond to the coupling interval, although this may vary according to coupling pattern and heart rate.[1 5]

Model behaviour

Simulation was performed using a range of cardiac burst magnitudes, and for *HR/fi* values over the general distribution determined for intra-operative anaesthetized, spontaneously breathing subjects.[5] Simulations were also performed with variations in Φ(I) slope and with RSA. Φ(I) slope variations were examined in the region 0–0.02.

In examining the model behaviour we determined (1) the range of coupling interval patterns generated, (2) the regions of the *HR/fi* plot associated with each coupling pattern, (3) the difference between intrinsic and observed breathing frequency, and (4) the specific pattern of ventilatory variation associated with each coupling pattern.

Simulation of human time series

Data were taken for study from material used in previous papers on cardioventilatory coupling,[5] from subjects showing clear pattern I, II, III, IV, or uncoupled RI interval plots or transitions between coupling patterns. Simulations were performed by using the patient's own heart rate time series and adding values for *fi* and burst magnitude into the model. To remove the effect of RSA the real heart rate time series was first filtered using a simple n beat, boxcar moving averager, where n is the closest integer to mean *HR/fo* ratio. From this filtered time series, a Φ(C) slope time series was calculated (Φ(C) slope=60/HR) and this was used to vary heart rate during simulation. For these simulations, we therefore knew both HR and *fo*, but burst magnitude and *fi* were unknown. Once we understood the relationship between *fi*, *fo*, burst magnitude and the specific coupling pattern (see results below), it was comparatively simple to determine approximate burst magnitude and *fi* values.

Nomenclature

The plot of *HR/fi* can be divided into a series of radiating areas between lines of integer relationship. To describe the distribution of coupling patterns on this plot, we term the area between any pair of consecutive integer ratio lines as the 'domain' of the lower integer ratio. Coupling pattern regions within each domain will be termed 'zones', indicated by an appropriate superscript. Thus, the area between 2:1 and 3:1 integer ratio lines is the 2:1 domain and a zone within this domain in which pattern I is generated is denoted I^2.

Results

Coupling patterns

Coupling patterns I, III, and IV were readily reproduced and were the most commonly observed patterns over a wide range of burst magnitude, HR and *fi* values. In Figure 2, we illustrate the simulated coupling patterns alongside comparable clinical recordings. In Figure 3 we show the distribution of these patterns over a map relating burst magnitude against the ratio *HR/fi*. Within each domain the relationship between coupling pattern, burst magnitude and *HR/fi* is qualitatively similar, although the range of burst magnitudes at which the various patterns occur differs with domain.

In addition to pattern I, III and IV, three zones of differing coupling type were also observed, two large areas A, B, and a smaller area C. Patterns A and B were similar to pattern III in that they exhibited multiple horizontal bands in the RI plot. However, unlike pattern III they were more complex, with a greater number of bands and these changed in appearance with small changes in HR, M_{Bc} or *fi*. In comparing these simulated patterns A and B, with real epochs of data, brief periods of similar pattern were observed although generally were transient. In the rabbit, we have previously described, and illustrated, stable periods of such patterns with eight bands in the 2:1 domain.[2] If noise was applied to *fi* by adding Φ(I) slope variability, the rapid changes in patterns A and B gave the appearance of their being entirely uncoupled.

The smaller zone, C, was observed sandwiched between the zones for pattern III and I. Retrospectively examining epochs of human data, this pattern was found in a number of human time series. Two examples are shown in Figures 2 and 7.

Within each domain, there are two pattern IV zones, which we term IV_{hi} and IV_{lo}. Corresponding to the patterns seen in clinical time series, the RI_1 interval progression for pattern IV_{hi} is downgoing and IV_{lo} upgoing (Fig. 2).

In Figure 4, we show the RI interval plots for a range of cardiac burst magnitudes and *HR/fi* ratios. For burst magnitudes in the range 0–0.2, patterns III and IV will occur commonly in the lower domains (between 2:1 and 4:1 *HR/fi*) but with increasing *HR/fi*, these patterns occur less commonly. For any particular burst magnitude there is a 'critical domain' or *HR/fi* ratio, in which patterns III and IV are no longer apparent and above which only pattern I will

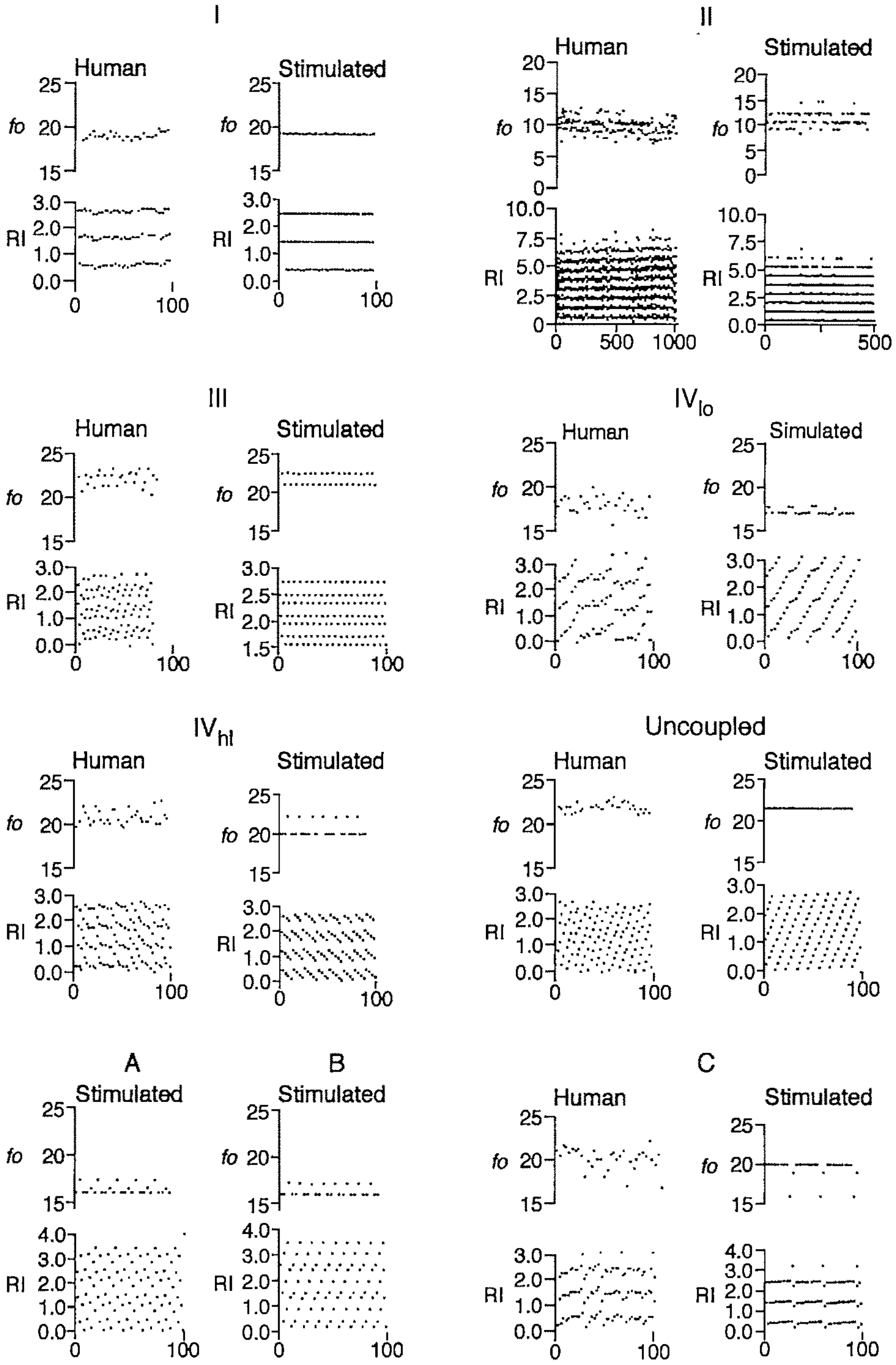

Fig 2 Representative examples of RI interval and observed breathing frequency time series showing simulated examples alongside similar patterns from real clinical time series.

occur. The domain in which this occurs will vary directly with burst magnitude.

If burst magnitude is held constant and the ratio HR/*fi* is allowed to progress through a domain, from the higher to lower integer relationship line, a sequence of pattern zones will be encountered which will differ according to both domain and burst magnitude. Thus, in the 3:1 domain at a burst magnitude of 0.075, HR/*fi* progresses through zones IV$^3_{hi}$, A^3, III^3, B^3, IV$^3_{lo}$ and I^3, whereas for a burst of 0.15, the progression is IV$^3_{lo}$, III^3, C^3 and I^3.

These pattern zones may also be represented on the map of HR versus *fi*. Figure 5A shows the zones as radiations on the HR/*fi* map for the burst magnitude 0.15. The width and presence of these radiations will vary according to burst

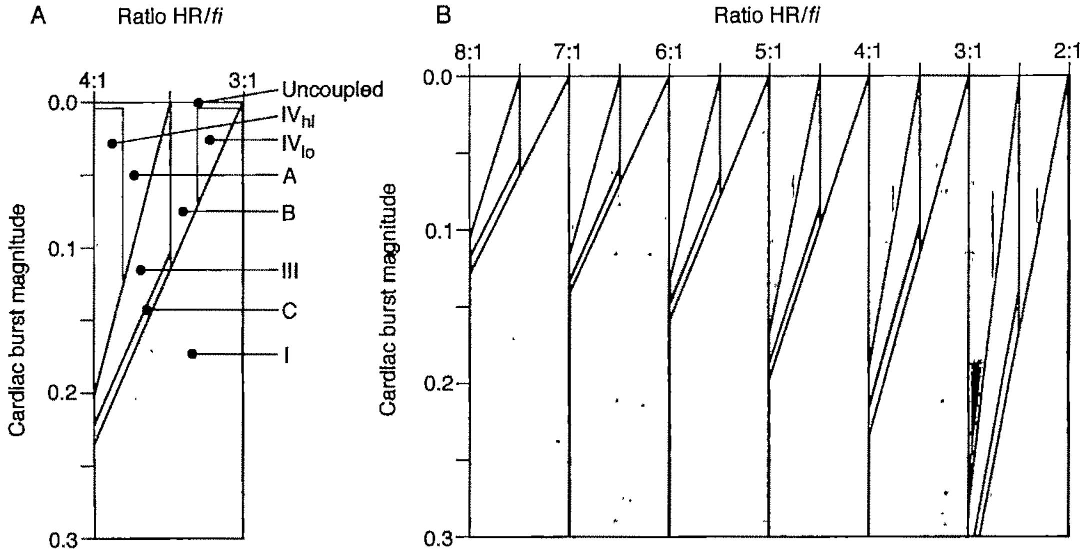

Fig 3 Pattern zones on the map of HR/*fi* *vs* M_{Bc} for (A) 3:1 domain and (B) between the 7:1 and 2:1 domains.

magnitude. This figure also illustrates the diminution of III and IV zones, and the invariability of pattern I coupling, at higher domains.

Intrinsic versus observed breathing frequency

Because cardiac triggered breaths occur earlier than intrinsic breaths, coupling makes the mean observed breathing frequency greater than the intrinsic rate and causes the observed breathing frequency to vary from breath to breath depending upon the pattern of coupling. To illustrate how observed frequency varies, we show, in Figure 5, the effect of allowing the HR to decrease from 75 to 50 beats min^{-1} while *fi* remains constant at 25 bpm. The HR/*fi* relationship moves from the 3:1 to 2:1 integer relationship line, through the 2:1 domain, passing through a sequence of pattern zones. The exact sequence of zones will vary, according to burst magnitude. If burst magnitude is 0.15 the sequence of zones is $\mathrm{IV}^2_{\mathrm{hi}}$, A^2, III^2, C^2, and I^2. If burst magnitude is 0.05 the sequence is $\mathrm{IV}^2_{\mathrm{hi}}$, A^2, III^2, B^2, $\mathrm{IV}^2_{\mathrm{lo}}$, and I^2. As HR/*fi* moves between these zones, the coupling pattern changes, as also does the pattern of inspiratory timing (*fo*).

Starting from the 3:1 integer relationsip line, where *fo*=*fi*, the HR/*fi* relationship moves across the zone. During its passage, the value of *fo* jumps to and fro between *fi* and a greater value, with *fo* increasingly taking on the greater value as HR falls. Mean *fo* therefore becomes increasingly greater than the starting *fi* value. The fluctuation in breathing frequency in Figure 5 is seen to be less than the horizontal interval between integer ratio lines. As this horizontal distance corresponds to a variation in ventilatory period of one heart period, pattern $\mathrm{IV}^2_{\mathrm{hi}}$ ventilatory period variability is associated with variations of less than one heart period. It can be seen in Figure 5 that the maximum magnitude of these ventilatory variations are equal to the horizontal width of the pattern I^2 zone where the HR/*fi* will later cut the transition between $\mathrm{IV}^2_{\mathrm{lo}}$ and I^2. The variation in breathing frequency will therefore be proportional to burst magnitude (which determines the width of the pattern I zone). Thus, the breathing frequency variation for M_{Bc}=0.15 is considerably greater than that for 0.05. In general, the mean breathing frequency during a pattern $\mathrm{IV}^2_{\mathrm{hi}}$ epoch will vary within an area of the 2:1 domain on the HR/*fo* map, a little below the 3:1 integer ratio line.

Passing through A^2, where breathing variation diminishes from that in $\mathrm{IV}^2_{\mathrm{hi}}$, HR/*fi* moves into the pattern III^2 zone, where breathing rate begins to alternate with consecutive breaths, again with a jump in ventilatory period of less than one heart period. Initially the quantal variability is of similar magnitude to that in the preceding pattern $\mathrm{IV}^2_{\mathrm{hi}}$ zone but decreases as HR falls. When the HR/*fi* ratio falls to an exact half integer, the breathing rate variation of pattern III^2 is zero. On the HR/*fo* map, the observed breathing frequency variation for pattern III^2 is now occupying the central region of the 2:1 domain.

From the pattern III^2 zone the HR/*fi* passes via B^2 into pattern $\mathrm{IV}^2_{\mathrm{lo}}$ if M_{Bc}=0.05 or directly into C^2 if M_{Bc}=0.15. The maximum *fo* variability in B^2, $\mathrm{IV}^2_{\mathrm{lo}}$ and C^2 are of similar magnitude to that in the $\mathrm{IV}^2_{\mathrm{hi}}$ zone although the specific pattern of variability differs between coupling patterns. In both C^2 and $\mathrm{IV}^2_{\mathrm{lo}}$, *fo* increasingly takes on the maximum value. On the HR/*fo* map, the observed breathing frequency variation is now occupying the lowermost region of the 2:1 domain.

As the HR/*fi* passes into the pattern I^2 region, *fo* is 'captured' by the 2:1 integer relationship line. The *fo* initially takes on a value equal to the maximum which was observed in the $\mathrm{IV}^2_{\mathrm{hi}}$ and $\mathrm{IV}^2_{\mathrm{lo}}$ zones. The displacement of *fo* from *fi* is greatest at this transition and can be seen to be proportional to burst magnitude. Remaining on the integer

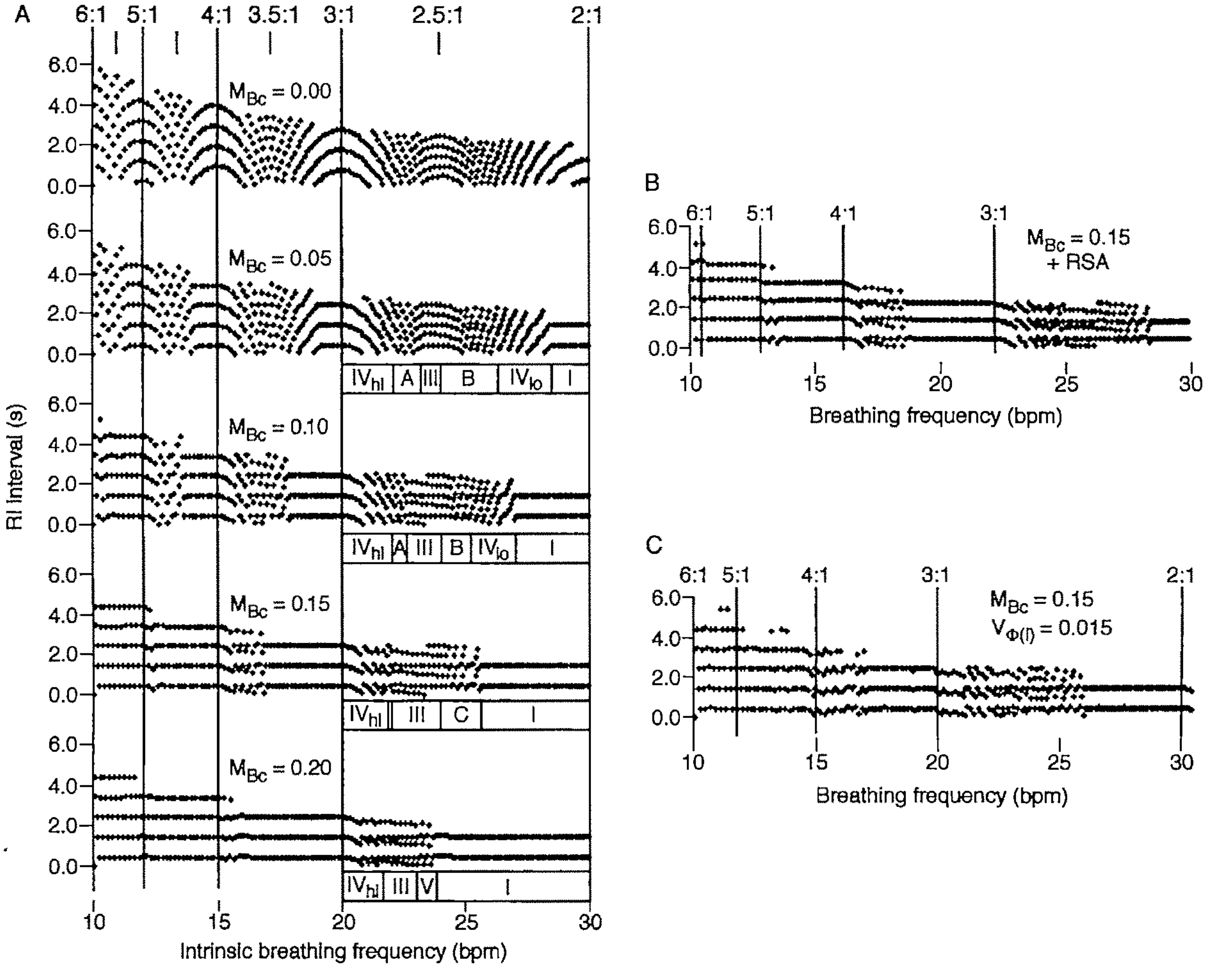

Fig 4 RI interval plots with constant HR=60 beats min^{-1} and *fi* increasing from 10 to 30 bpm. (A) The effect of increasing M_{Bc} on coupling pattern for values of M_{Bc} between 0 and 0.20. Note that as M_{Bc} increases the region occupied by pattern I coupling increases, and that this increase is more marked in higher domains. (B) The effect of adding RSA, although HR has changed there is little qualitative difference in RI plot. (C) Effect of adding $V_{\Phi(I)}$=0.02 to Φ(I), showing the generation of pattern II in the 5:1 and 4:1 domains.

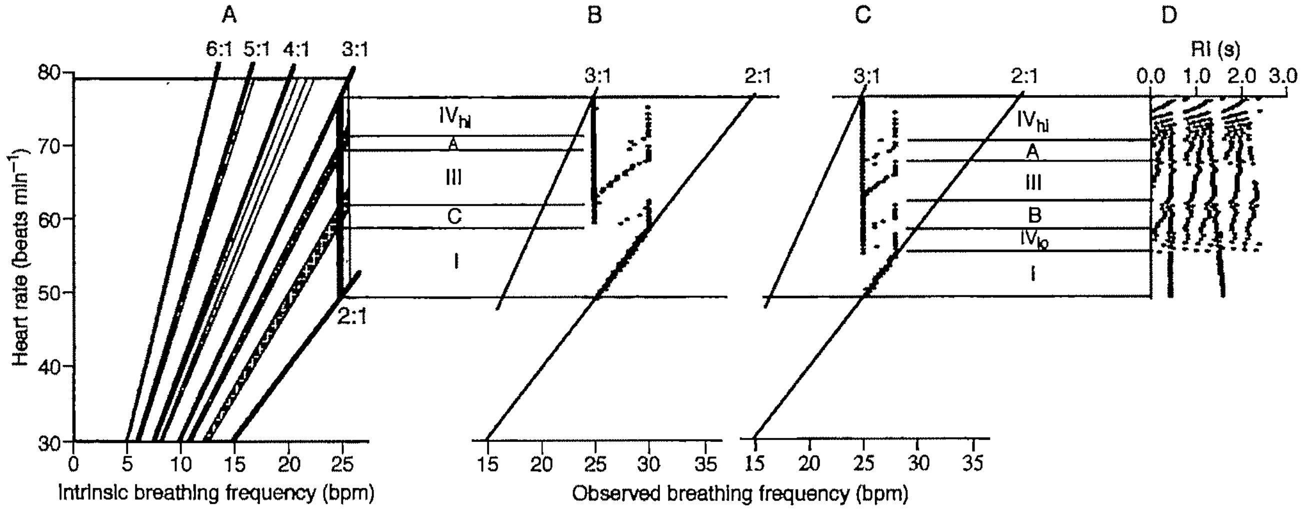

Fig 5 (A) HR/*fi* map for M_{Bc}=0.15. With simulation at *fi*=25 bpm, heart rate is decreased from 75 (3:1 IRL) to 50 beats min^{-1} (2:1 IRL) indicated by the vertical bar. The sequence of pattern zones encountered is IV_{hi}, A, III, and I. The resulting observed breathing frequency, *fo*, is shown in (B). With the same simulation re-run for M_{Bc}=0.05 the sequence of pattern zones is IV_{hi}, A, III, B, IV_{lo} and I. The resulting observed breathing frequency and corresponding RI plot are shown in (C) and (D) respectively.

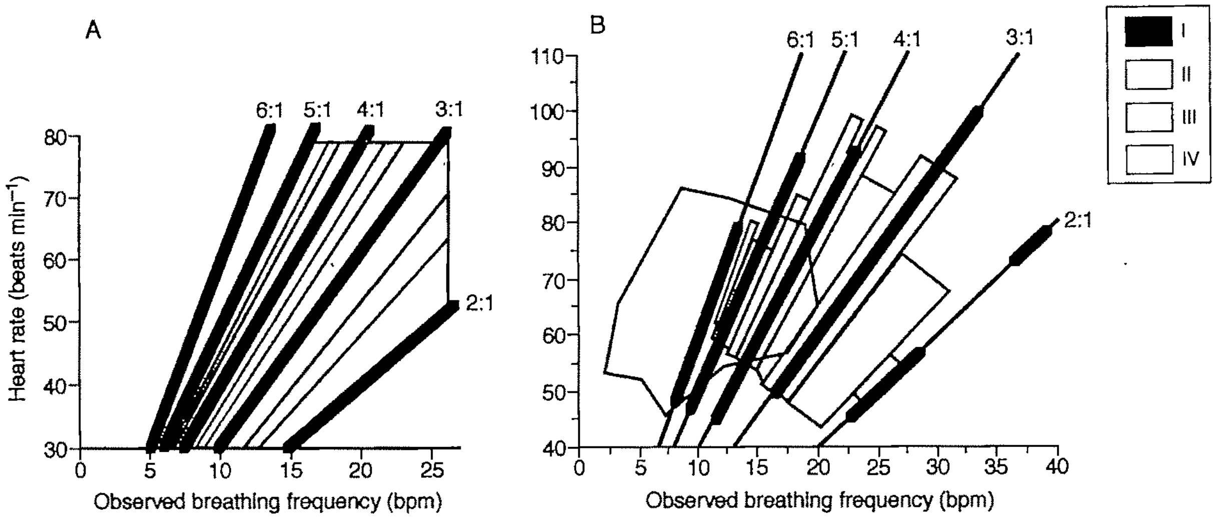

Fig 6 Using the observed breathing frequencies in Figure 4. (A) Schematic diagram of the coupling pattern zones plotted on the map of HR *vs fo* map. This map is qualitatively similar to that observed in anaesthetised human subjects (B), which was generated from data by Galletly and Larsen.[5]

relationship line the value of *fo* continues to smoothly decrease as HR falls until HR/*fi* intersects the 2:1 integer relationship line at which time *fo* will once again equal *fi*. Thereafter a sequence of pattern zones in the first domain would be encountered.

From these observations, we can compare the coupling pattern distribution on the maps of HR/*fi* and HR/*fo*. The HR/*fi* map shows radiations corresponding to the four pattern zones, but because *fo* is altered by the coupling pattern, the pattern distribution on the HR/*fo* map is different. Pattern I occupies only the integer relationship lines, pattern III occupies the central regions of these domains and pattern IV_{hi} and IV_{lo} occupy regions adjacent to the integer relationship lines. The simulated pattern distribution of the HR/*fo* map is therefore qualitatively similar to that which is observed in the anaesthetised human subject (Fig. 6).

Pattern II

In clinical samples, pattern II coupling is seen primarily from the 4:1 domain upwards and from 6:1 it is the only pattern observed. In human epochs of pattern II, all breaths are initiated by cardiac related activity (as RL_1 is constant) and because entrainment ratio varies in an apparently random manner, consecutive breaths may show a sequence of, for example 5,7,5,5,6,7,5 entrainment. This form of coupling implies, in our model, that inspiratory onset is always cardiac burst related but may be initiated after a different number of cardiac bursts from breath to breath. In simulation, we observed that when a small random variation was applied to the $\Phi(I)$ slope at low ventilatory rates (i.e. higher domains), pattern II coupling was readily produced (Figs 2 and 4). Thus variability of $\Phi(I)$ and probably also HR or burst magnitude, causes variation in the specific cardiac burst which achieves threshold crossing. Because of the steeper $\Phi(I)$ slope, similar degrees of variation at higher breathing rates generally did not disrupt the I, III, and IV patterns to any great extent. Thus above the critical domain at which pattern I is invariable, noise in the system changes these invariable pattern I domains into pattern II. We conclude therefore that pattern II can be accounted for by (a) the invariability of a cardiac burst initiating the threshold crossing when $\Phi(I)$ slope is low together with (b) small variations in $\Phi(I)$ slope, HR or burst magnitude.

As seen in clinical samples, the breathing frequency variability during pattern II coupling was observed in simulation to be characterised by quantal jumps in ventilatory period corresponding to changes in entrainment ratio. Thus, changes in ventilatory period occurred in multiples of the heart period.

The distribution of coupling types seen in the HR/*fo* map of anaesthetised subjects (Fig. 6) can therefore be entirely explained by our model. Pattern II is invariably present above a critical boundary domain, below which patterns I, III, and IV occur in radiating zones.

Respiratory sinus arrhythmia

Other than the associated increase in HR caused by reducing the cardiac threshold, the addition of RSA had no major qualitative effect on the HR/f distribution of coupling patterns or *fo* variability (Fig. 4).

Simulation of human time series

Although the qualitative behaviour of our model is similar to that observed in human subjects, it would be of considerable interest to demonstrate whether the model can simulate clinical observations exactly. Unfortunately, in clinical data we observe *fo*, HR and the RI interval variation, but the two variables *fi* and burst magnitude are unknown. To simulate the patterns of coupling and *fo* variability from real data we, therefore, need to choose suitable values for *fi*

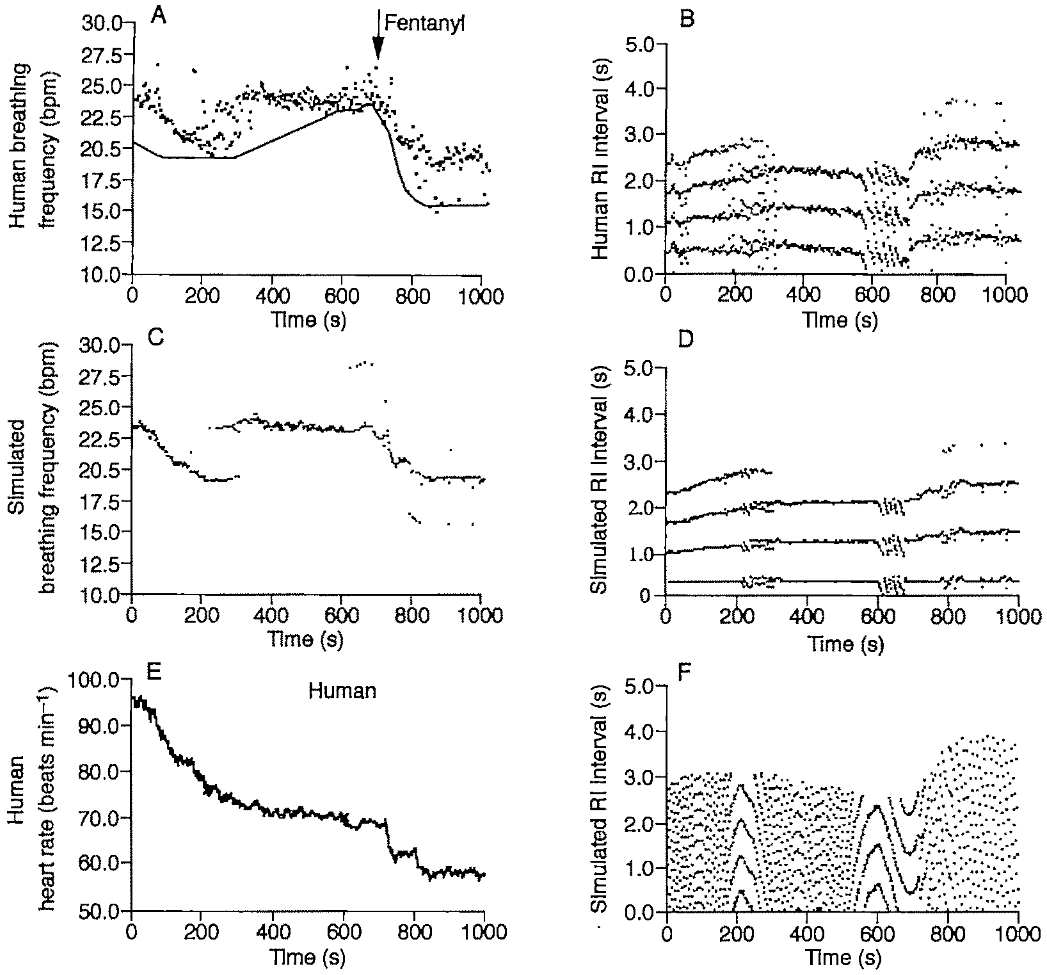

Fig 7 Comparison of a human and simulated RI interval plot and breathing frequency time series. A hypothetical explanation for this epoch was given by Galletly and Larsen.[5] The time series is for an anaesthetised subject given fentanyl at time 720 s. (A) Human observed breathing frequency time series and estimated input values for intrinsic breathing frequency used for simulation. (B) The associated human RI interval time series showing progression through patterns I^4, III^3, I^3, IV^2_{hl} I^3 and C^3. In Galletly and Larsen,[5] the C^3 segment was classified originally as pattern II, but is almost certainly associated with the pattern C zone. Input variables for simulation were *fi* as in (A), M_{Bc}=0.175 increasing to 0.2 at 720 s and filtered HR time series (E). The resulting simulated breathing frequency time series (C) and simulated RI interval plot (D) bear a remarkable similarity to the human data. In (F) we show the same simulation but in the absence of cardiac bursts (i.e. M_{Bc}=0).

and burst magnitude. From the foregoing observations, several pointers are available to guide our choice of values:

Burst magnitude

(1) If there were no sudden transitions in heart rate or ventilatory frequency we could assume that the HR/*fi* relationship would wander smoothly through regions of the HR/*fi* versus burst magnitude map. A crude guide to burst magnitude could, therefore, be obtained if some transitions between patterns only occur in certain burst magnitude ranges. Thus, IV^2_{lo} only occurs at low burst magnitudes and a rapid transition between IV^2_{hi} and I^2 via pattern C^2, will only occur at high burst magnitudes
(2) Burst magnitude could be inferred from the magnitude of the maximum breathing frequency variation during pattern IV.
(3) The bands in the pattern III RI plot are evenly separated when burst magnitude is small but more closely grouped into pairs as burst magnitude increases. Close groupings therefore suggest a high burst magnitude.

Intrinsic breathing frequency

The longest ventilatory period will correspond to that preceding an intrinsic Φ(I) triggered breath. For those patterns where the mechanism of inspiratory triggering varies between breaths (patterns III, IV, A, B, and C), the lowest breathing frequency will, therefore, correspond to *fi*. Unfortunately a pure pattern I (or II) epoch gives no obvious clues as to its control variables as all breaths are cardiac triggered and any combination of burst magnitude and *fi* falling within a pattern I zone gives the same HR/*fo*.

Using these observations, we could recreate the observed breathing patterns and RI plots of human subjects using the subject's own heart rate time series and inferred *fi* and burst magnitude values. In all clinical time series, which we have examined, agreement between the real and simulated RI

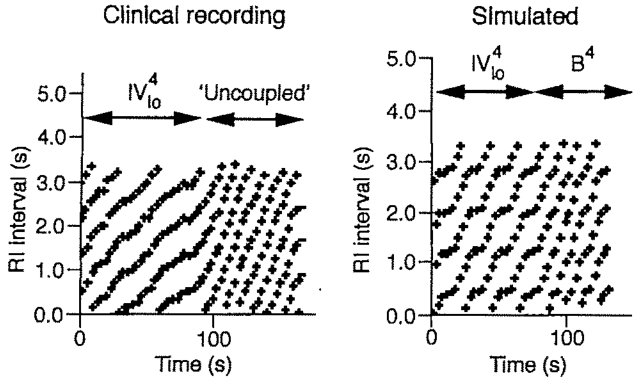

Fig 8 An RI plot transition between pattern I and what appears to be uncoupled. Using the patients' own heart rate time series and an M_{Bc} of 0.05 the simulated RI plot shows a transition between pattern IV and the more complex pattern B. This suggests that epochs which appear uncoupled may at times represent patterns A or B with added 'noise'.

plots could be obtained by appropriate selection of burst magnitude and *fi*. An example is shown in Figure 7, where the simulation is consistent with the explanation given for this time series in our previous paper.[5] In simulations, the required burst magnitude varied between individuals explaining why some clinical time series show a variety of patterns despite similar heart and breathing frequencies. In addition, because these HR time series are RSA filtered, it is clear that RSA, although undoubtedly contributing to minor variations of RI and breathing frequency variation, does not play a critical role in the mechanism of coupling.

In Figure 8, we have modelled a transition between pattern IV and what appears to be uncoupled. The simulation revealed a similar transition but clearly indicates that what appears to be uncoupled may at times be the complex, multiple banded patterns A or B, presumably with the addition of 'noise'.

Discussion

This model of cardioventilatory coupling is consistent with observations of coupling and ventilatory variability during spontaneous breathing general anaesthesia. The model explains observed patterns of coupling and predicted variations of these patterns, which were subsequently found in clinical time series. The model satisfactorily explains why coupling is invariable above a critical boundary region, and the distribution of coupling patterns on the map of HR/*fo* for clinical data. The simulation is consistent with clinically observed breathing variation associated with each coupling pattern and allows reproduction of both RI plots and ventilatory variability from the heart rate time series of human subjects.

From our clinical observations and from the clinically consistent behaviour of the model we can, therefore, elaborate on the preliminary hypothesis[5] put forward for the generation of coupling, coupling patterns and intraoperative breathing irregularity.

In our hypothetical model, inspiration occurs when the activity of an intrinsic pacemaker function reaches an inspiratory firing threshold. The likelihood of this function crossing the firing threshold increases in response to a signal of cardiac origin, and therefore, the exact timing of inspiratory onset will vary according to whether the intrinsic pacemaker function crosses the threshold or whether an earlier cardiac signal causes threshold crossing. Depending upon the ratio of HR to *fi*, and the magnitude of the afferent cardiac signal, the sequence of consecutive threshold crossings (cardiac triggered versus intrinsic) will vary, and these variations are seen as the observed coupling patterns and corresponding breathing rate irregularities.

Pattern I

Consecutive inspirations are all initiated by the cardiac stimulus and the same number of heart beats occur within each ventilatory period (i.e. the entrainment ratio is constant). Pattern I occurs when HR/*fi* is in the range where consecutive leading edges of the cardiac burst cause inspiratory threshold crossing. If the magnitude of the cardiac stimulus is low, pattern I coupling only occurs when the HR/*fi* ratio is equal to, or a little over an integer value. However, as the cardiac stimulus intensity increases, pattern I occurs over a wider range of HR/*fi* values within a domain. The critical HR/*fi* above which pattern I is invariable (or because of 'noise' pattern II) occurs, in our model, when the tip of one cardiac burst exceeds the base of the following cardiac burst (Fig. 1). It can be shown from simple geometry that in a simple linear model, this critical boundary occurs at HR/*fi*=1/burst magnitude. Breathing frequency variability during pattern I coupling is negligible because entrainment ratio is constant and ventilatory period equals the interval between burst related crossings of the inspiratory threshold.

Pattern II

Pattern II is a variant of pattern I in which small variations in Φ(I) slope (and/or HR and burst magnitude) cause variation in the entrainment ratio. The effect of Φ(I) slope variation is greatest when Φ(I) slope is least and hence pattern II is most common at high HR/*fi* ratios or low breathing rates. Varying entrainment ratios cause quantal variation in breathing frequency corresponding to one or more multiples of the heart period.

Pattern III

Consecutive inspirations alternate between intrinsic and cardiac triggering. Ventilatory period also alternates with this variation; the alternate ventilatory periods are (i) from the cardiac burst crossing to intrinsic crossing and (ii) from the intrinsic crossing to cardiac burst crossing. The ventilatory period between a cardiac triggered breath and a following intrinsic breath will correspond to *fi*, whereas the interval from an intrinsically triggered inspiration to one that is cardiac triggered will be shorter. The magnitude of this variation from breath to breath is less than one heart period. It follows from this that the slowest observed frequency seen during pattern III variation will correspond to the intrinsic breathing frequency (*fi*).

Pattern IV

Cyclical periods of intrinsic inspiratory triggering follow periods of cardiac burst related triggering. Breathing rate varies according to the phase of this cycle although the largest variation will occur when a cardiac burst related breath changes to an intrinsic triggered breath. The minimum *fo* during a period of pattern IV coupling will occur during the phase of consecutive intrinsic crossings. Thus, as with pattern III, the intrinsic breathing frequency will correspond to the slowest observed frequency. The magnitude of the breathing frequency variation will be directly proportional to the magnitude of the afferent cardiac signal.

'Uncoupled'

Apparently uncoupled patterns are generated under two circumstances. (i) If burst magnitude is small and the majority of breaths are initiated by the intrinsic $\Phi(I)$. Small degrees of breathing frequency variability under this circumstance may occur because of 'noise' and occasional cardiac burst related triggerings. (ii) At higher burst magnitudes apparently uncoupled time series may be generated during complex patterns A and B which have been disrupted by small variations in HR, burst magnitude, *fi* and coupling interval.

The described model structure is remarkably similar to that proposed over 20 yr ago by Cohen and Feldman[6] in order to explain the effects of electrical stimulation of certain brain regions on inspiratory timing. In their model, the slope of a hypothetical inspiratory function (also Φ) was increased or decreased by electrical stimulation of the rostral or ventral part of the nucleus parabrachialis, respectively. Delay or shortening of the expiratory—inspiratory phase switch could be achieved by such stimulation. Within the framework of Cohen's model, cardioventilatory coupling might be viewed as an example of pulse synchronous rostral stimulation. It may therefore be relevant that the nucleus parabrachialis is the main relay for visceral traffic from the nucleus tractus solitarius to forebrain structures.[7] As the nucleus tractus solitarius is the main site of termination of afferent cardiovascular receptors it is conceivable that this region could mediate coupling related cardiovascular stimulus.

An important component of our model is the presence of an intrinsic inspiratory pacemaker. A pacemaker such as this is well recognized, with spontaneous pacemaker activity being measured in isolated brain stem regions associated with respiratory activity. However, it is also known that the frequency of this pacemaker is slower than that in intact animal preparations. The pre-Botzinger complex of the isolated rat brain stem has an intrinsic frequency approximately one third that of the normal breathing rate and, in intact preparations, brain stem de-afferentation reduces breathing frequency.[8] If, as many authors believe, the pre-Botzinger complex pacemaker is the origin of the breathing rhythm, a mechanism must exist which augments the intrinsic activity and increases the frequency of the core oscillator. A key feature of our model is the shortening of intrinsic ventilatory period by the cardiac afferent stimulus and therefore this might, in part, explain a mechanism for this augmentation. Furthermore, both somatic stimulation and locomotor activity are also capable of entraining the respiratory rhythm.[9–11] Perhaps therefore cardioventilatory coupling simply represents one aspect of a general mechanism whereby an intrinsic respiratory pacemaker is augmented by a number of afferent inputs. Such a mechanism could relate to a variety of clinical observations including the ventilatory responses to stimulation and exercise.

Although ample evidence suggests the presence of an intrinsic respiratory pacemaker, and the presence of coupling suggests some form of interacting cardiovascular signal, we stress that the described model need not have exact neuroanatomical or electrophysiological correlates. The model is one that behaves in a similar manner to that of the intact anaesthetized human inspiratory timing mechanism, and as such, may be useful for predicting behaviour. It should be used with caution, however, for understanding the detailed underlying mechanisms. The quantity 'cardiac burst magnitude' represents a process whereby the value of $\Phi(I)$ and the inspiratory firing threshold are transiently brought closer together. This process could also have been brought about by other means with no change in the overall behaviour. Thus, the afferent cardiac signal could equally reduce inspiratory threshold instead of cardiac bursts augmenting $\Phi(I)$. Each variant does not differ in its overall behaviour and hence could equally be considered as models of inspiratory timing. However, certain features of the model are invariant, that is, present irrespective of how the model is constructed. Perhaps the most important of these is the central idea that a cardiac triggered breath will always be shorter than the intrinsic breath, which would have occurred if the cardiac signal had not been present. The effect of coupling in the model is always to increase the mean observed frequency over the intrinsic. This property has the potential for two clinical implications.

Cardioventilatory 'overdrive'

In some regions of the HR/*fi* map (especially at high *fi*, high burst magnitude and at the boundary of patterns IV_{1o} and I), *fo* may be 'driven' at rates well in excess of *fi*. From our analysis, as HR/*fi* crosses from a IV_{lo} to I zone, the HR/*fo* will be forced, at the same heart rate onto the next lowest integer relationship line. Thus, at HR=80 and *fi*=30, the HR/*fi* ratio is 2.66. If cardiac bursts are of sufficient magnitude to place this HR/*fi* ratio into a pattern I zone the resulting HR/*fo* would equal int2.66=2. As HR remains at 80 and HR/*fo*=2, the breathing frequency will increase from 30 to 40 bpm. Unexpectedly high breathing rates such as these are occasionally seen in anaesthetized subjects in the absence of opioids and may in part be a result of this cardioventilatory 'overdrive'. It might be expected that if breathing frequency is driven in this manner for any length of time, with constant tidal volume, there will be a chemoreceptor mediated adjustment of minute ventilation to a lower value. Whether a resetting of intrinsic breathing frequency occurs or whether tidal volume falls in response to a sustained coupling related frequency overdrive, needs to be determined experimentally. However, if a resetting of intrinsic frequency occurred it would be expected that pattern I could not be sustained for long periods as the *fi* resetting will cause the HR/*fi* to move back into the IV_{lo} zone and hence reduce mean breathing frequency. In our clinical time series, some subjects were observed to remain in pattern I, locked onto the integer relationship line for periods of 5 min or longer suggesting that minute ventilation is being adjusted in these subjects by changes in tidal volume, rather than through adjustment in *fi*.

Cardioventilatory 'support'

The potential for excessively high breathing frequencies can be contrasted to the effect of coupling at low intrinsic breathing frequency. At low simulated breathing rates, the $\Phi(I)$ slope is comparatively flat, and because all breaths at rates less than 10–12 bpm are cardiac burst initiated, coupling is invariably present (as pattern I or II). It follows therefore that at low breathing rates the mean observed breathing frequency will always be greater than the intrinsic frequency. Figure 7 demonstrates this supporting effect of coupling in a human time series. After the administration of fentanyl, the opioid, presumably by an effect on the inspiratory pacemaker, has reduced *fi* to approximately 15.5 bpm (we can infer *fi* because, as noted above, the minimum *fo* will correspond to *fi* in patterns III, IV, A, B, C). The cardiac triggered breaths however are of higher breathing frequency and, as the breathing frequency jumps between cardiac and intrinsic triggered breaths the mean breathing frequency is increased to approximately 19 bpm. During opioid mediated depression of the intrinsic inspiratory pacemaker, therefore, cardiac afferent activity supports breathing frequency at values greater than that of the intrinsic pacemaker. Whether such support is clinically relevant remains to be determined. As noted above, the regulation of breathing involves the control of minute ventilation by alteration of both rate and tidal volume. However, a mechanism that is relevant to the control of frequency should be of clinical interest as central apnoea is a failure of frequency control. Because cardioventilatory coupling provides a simple non-invasive indication of frequency control which is not otherwise accessible, we suggest that observations of coupling (cardiac, somatic and locomotor) in subjects with abnormal control of respiratory frequency may be helpful.

In previous papers, we have attempted to quantify coupling in terms of the constancy of the RI_{-1} interval (the interval between the inspiration and the preceding R wave). This constancy was measured as the proportional Shannon entropy of the RI_{-1} interval (H_{RI-1}). This quantity varies according to coupling pattern, with the most disordered RI plots (i.e. those that are uncoupled) having higher H_{RI-1}values than those that are perfectly ordered (pattern I). H_{RI-1} varies with pattern according to the order: I = II < III < IV < uncoupled. Although intuitively H_{RI-1} may be considered a measure of 'strength of coupling' our model clearly indicates that the true strength of coupling must be burst magnitude and that this cannot be directly equivalent to H_{RI-1}. Thus, two individuals may have identical burst magnitudes and very similar HR/*fi* ratios but if one falls into a pattern I zone the H_{RI-1} will be low whereas the other, with a fractionally different HR/*fi*, may fall into a pattern III or IV zone and hence the H_{RI-1} will be high. As the burst magnitude is identical in these subjects, the underlying strength of interaction between the cardiac afferent and the respiratory pacemaker is the same. Measures based on the RI interval variation such as H_{RI-1}, should be distinguished from the true strength of signal interaction (cardiac burst magnitude). Differences in coupling pattern (and hence H_{RI-1}) may be caused by minute changes in HR/*fi* and not by the changes in the strength of interaction between the cardiac afferent and the intrinsic pacemaker. To observe a true alteration in the strength of cardiac afferent/respiratory interaction, or to infer a intrinsic disorder of coupling, demands the observation of altered burst magnitude rather than a simple comparison of coupling pattern or RI plot. We describe several strategies for determining the magnitude of the cardiac afferent signal.

Acknowledgements

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References

1 Galletly DC, Larsen PD. Cardioventilatory coupling during anaesthesia. *Br J Anaesth* 1997; **79**: 35–40

2 Larsen PD, Galletly DC. Cardioventilatory coupling in the anaesthetised rabbit, rat and guinea pig. *Pflugers Archiv* 1999; **437**: 910–6

3 Coleman WM. On the correlation of the rate of heart beat, breathing, bodily movement and sensory stimuli. *J Physiol* 1921; **54**: 213–7

4 Raschke F. Coordination in the circulatory and respiratory

systems. In: Rensing L, an der Heiden U, Mackey MC eds. *Temporal Disorder in Human Oscillatory Systems*. Berlin: Springer-Verlag 1987; 152–75

5 Galletly DC, Larsen PD. Ventilatory frequency variability during spontaneously breathing anaesthesia. *Br J Anaesth* 1999; **83**: 552–63

6 Cohen MI, Feldman JL. Models of respiratory phase switching. *Fed Proc* 1977; **36**: 2367–74

7 Dampney RAL. Functional organisation of central pathways regulating the cardiovascular system. *Physiol Rev* 1994; **74**: 323–64

8 Rekling JC, Feldman JL. Prebotzinger complex and pacemaker neurons: hypothesized site and kernel for respiratory rhythm generation. *Annu Rev Physiol* 1998; **60**: 385–405

9 Bramble DM, Carrier DR. Running and breathing in mammals. *Science* 1983; **219**: 251–6

10 Iscoe S. Respiratory and stepping frequencies in conscious exercising cats. *J Appl Physiol* 1981; **51**: 835–9

11 Iscoe S, Palosa C. Synchronization of respiratory frequency by somatic afferent stimulation. *J Appl Physiol* 1976; **40**: 138–48

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Survey of cancellation rate of hypertensive patients undergoing anaesthesia and elective surgery

P. Dix* and S. Howell

Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW, UK
**Corresponding author: Department of Anaesthesia, Southmead Hospital, Westbury on Trym, Bristol BS10 5NS, UK*

Hypertension is the commonest avoidable medical indication for postponing anaesthesia and surgery. There are no universally accepted guidelines stating the arterial pressure values at which anaesthesia should be postponed. The aim of this study was to determine the extent of variation across the South-West region of the UK in the anaesthetic management of patients presenting with stage 2 or stage 3 hypertension. Each anaesthetist in the region was sent a questionnaire with five imaginary case histories of patients with stage 2 or stage 3 hypertension. They were asked if they would be prepared to provide anaesthesia for each patient. The response rate was 58%. We found great variability between anaesthetists as to which patients would be cancelled. Departmental protocols may aid general practitioners and surgeons in the preparation of patients for surgery, but such protocols may be difficult to agree in the light of such a wide variation in practice.

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Arterial hypertension is common, affecting between 4 and 28% of patients presenting for major non-cardiac surgery.[1–3] Long-standing hypertension is associated with damage to the coronary, renal, and cerebral circulations. These end-organ changes may lead, in turn, to peri-operative cardiovascular complications.[4 5] Hypertension is certainly associated with an increased incidence of both pre-operative and post-operative silent myocardial ischaemia, which are significant predictors of adverse cardiac outcome.[6–8] A pre-operative history of hypertension has been shown to be associated with increased risk of peri-operative cardiovascular death in the non-cardiac surgery population.[9] However, a clear association has not been demonstrated between admission arterial pressure and major peri-operative cardiac complications.[5 10]

Initially, studies on hypertension and cardiovascular risk focused on diastolic hypertension. Increasing systolic pressure with age was regarded as a physiological rather than a pathological change. There were also concerns that treating raised systolic pressure would produce an unacceptable decrease in diastolic pressure that would compromise cerebral perfusion. However, in the general population, systolic hypertension is a more potent risk factor for cardiovascular morbidity than diastolic hypertension.[11] Recent work has shown that treating systolic hypertension reduces the risk of stroke and myocardial infarction in the elderly population.[12 13]

The Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCDET V), classified arterial pressure into four stages; stage 1 to stage 4 (Table 1).[14] It is widely accepted that patients with stage 1 hypertension have little or no increased risk of peri-operative cardiac morbidity[10] and, therefore, anaesthesia and surgery in such patients can proceed as planned. Similarly, patients with stage 4 hypertension are very likely to have severe end organ damage. Such patients represent a high risk of cardiac morbidity and a major anaesthetic challenge and, unless surgery is urgent, anaesthesia should be postponed to allow their markedly raised arterial pressure to be treated. The intermediate groups, who present for anaesthesia and surgery with stage 2 and stage 3 hypertension present more of a dilemma with regard to peri-operative management. There is a balance to be struck. On the one hand, there are the possible risks of anaesthesia and surgery in patients with raised arterial pressure. Set against these are the inconvenience and distress caused to patients by the cancellation of surgery at short notice and the waste of hospital resources.

There are no universally accepted guidelines stating the arterial pressure values at which anaesthesia should be

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Table 1 Classification of arterial pressure for adults aged 18 yr and older. When the arterial pressure falls in different categories of systolic and diastolic pressure the higher category applies. Fifth Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure[14]

Category	Systolic arterial pressure (mm Hg)	Diastolic arterial pressure (mm Hg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Hypertension		
Stage 1	140–159	90–99
Stage 2	160–179	100–109
Stage 3	180–209	110–119
Stage 4	≥210	≥120

postponed. Most textbooks quote a diastolic pressure of 110 or 115 mm Hg as a cut-off for postponing anaesthesia. This uncertainty sets the scene for wide variations in practice. Such variation can be a cause of confusion and uncertainty among general practitioners referring patients. for surgery, and among surgical teams referring patients for anaesthesia. The aim of the present study was to determine the extent of variation across the South-West region of the UK in the cancellation rate of patients presenting with stage 2 or stage 3 hypertension.

Methods

The study took the form of a postal survey to all the anaesthetists in the South-West Health Service region of the UK. Anaesthetists were sent a questionnaire with five imaginary case histories of patients with stage 2 or stage 3 hypertension and varying degrees of arterial pressure control and target organ damage. They were asked if they would be prepared to provide anaesthesia for each of these patients. Anaesthetic secretaries supplied details of anaesthetists working in each anaesthetic department in each hospital in the South-West region. A four-page questionnaire, covering letter and self-addressed envelope, was sent to each anaesthetist in the region. The questionnaire described five imaginary patients, presenting for elective surgery, with varying degrees of hypertension, symptoms, and evidence of target organ damage. Clinical details of the target organ damage were given as described below. We did not state if the patient had target organ damage, leaving the anaesthetist to deduce this. Arterial pressure readings were given, but not the stage of hypertension according to the JNCDET V classification (e.g. stage 1, stage 2 etc.). For each case a tick box response was allowed to indicate whether the anaesthetist would anaesthetize the patient as planned, or postpone the patient for further investigations or management. A box for free text comments was also provided at the end of the questionnaire. The questionnaire was anonymous. Information was collected on the grade of anaesthetist and the hospital in which they worked.

Case 1 had stage 2 hypertension with end-organ involvement. He was a 50-yr-old coal man presenting for a total knee replacement. He was said to be 5′10" tall, and weighed 95 kg. He was an ex-smoker, with no past medical history. He was on no medication and had no cardiovascular or respiratory symptoms.

On admission, his arterial pressure was 165/100 mm Hg, and did not settle on repeated measurement. An ECG showed left ventricular hypertrophy and strain changes (S wave V2 10 mm, R wave V5 25 mm, with inverted T waves in V4–V6). A full blood count, and urea and electrolytes were normal.

Case 2 had stage 3 hypertension that settled to stage 2 after admission. He had no evidence of end-organ involvement, but had other cardiovascular risk factors. He was a 55-yr-old TV executive presenting for a redo laminectomy at two spinal levels. He was said to be 6′1" tall, and weighed 98 kg. He smoked 20 cigarettes per day, and drank five glasses of wine per day. He had no past medical history, took no regular medications, and had no cardiovascular or respiratory symptoms.

On admission, his arterial pressure was 180/115 mm Hg, which settled to 165/105 mm Hg on subsequent measurements. His full blood count, and urea and electrolytes were within the normal range, and an ECG showed no abnormalities.

Case 3 had stage 3 hypertension that settled to stage 2 after admission. She had end-organ involvement. She was a 67-yr-old retired medical secretary presenting for an open cholecystectomy. She was said to be 5′3" tall, and weighed 86 kg. She was a non-smoker. Her only past medical history was a myocardial infarct 5 yr before. She reported shortness of breath on climbing stairs, but had no other cardiovascular or respiratory symptoms.

On admission, her arterial pressure was 190/105 mm Hg, which subsequently settled to 165/100 mm Hg. The full blood count was normal, and urea and electrolytes showed a creatinine of 125 μmol litre^{-1}. An ECG showed Q waves inferiorly.

Case 4 had isolated systolic hypertension. She had stage 3 hypertension with no end-organ involvement and no other cardiovascular risk factors. She was a 70-yr-old retired teacher presenting for total hip replacement. She was said to be 5′2" tall, and weighed 50 kg. She was a non-smoker, took no medication, and had no cardiovascular or respiratory symptoms.

On admission and subsequent readings, her arterial pressure was 200/85 mm Hg. A full blood count, and urea and electrolytes were normal, as was an ECG.

Case 5 had stage 2 hypertension with no end-organ involvement and no other cardiovascular risk factors. He was a 51-yr-old ex-professional footballer presenting for a total knee replacement. He was said to be 6′1" tall and weighed 91 kg. He was a non-smoker, who swam regularly. He had a 2-yr history of poorly controlled hypertension, for which he took nifedipine. He had no other past medical

Table 2 Results of postal questionnaire, showing numbers of anaesthetists prepared to anaesthetize each imaginary hypertensive patient

			Number (%) of anaesthetists prepared to anaesthetize case			
Case number	Hypertension Stage	End-organ disease	Total n=255	Consultants n=153	Non-training grade n=19	Trainees n=83
1	2	Yes	66 (25.9)	44 (29)	3 (16)	19 (23)
2	3, settled to 2	No	107 (41.9)	61 (40)	8 (42)	38 (46)
3	3, settled to 2	Yes	135 (52.9)	93 (61)	7 (37)	35 (42)
4	3	No	186 (73)	122 (80)	18 (95)	58 (70)
5	2	No	193 (75.6)	115 (75)	14 (74)	64 (77)

history, and his only other regular medication was diclofenac. He had no cardiovascular or respiratory symptoms.

On admission, his arterial pressure was 172/107 mm Hg, which subsequently settled to 164/101 mm Hg. A full blood count, and urea and electrolytes were normal, as was an ECG.

Data for all anaesthetists, consultant and juniors, were analysed together. A chi-squared test for trend was used to examine the trend in cancellation rate across the five cases. This trend was examined in detail by making pair wise comparisons between consecutive cases, using squared tests. Finally, for individual cases the responses of consultants and other staff were compared, again with chi-squared tests. It was noted that this involved multiple testing (five tests), and that positive results obtained in this context should be interpreted with caution.

Tests were performed using Epi-Calc2000 v1.02 running on a Viglen Pentium II 233MHz.

Results

A total of 488 questionnaires were sent out, of which 283 (58%) were returned. There were 255/488 (52.3%) usable replies. The remainder of the replies failed to report the hospital and/or grade of anaesthetist. Between hospitals, the response rate varied from 18/25 (72%) to 1/11 (9%). The responses are reported for each case history (Table 2).

Although the cases were not arranged in order of severity, a trend was noted such that the proportion of anaesthetists who deferred the patient decreased with each successive case. Comparisons between successive pairs of cases were statistically significant, except for that between case 4 and case 5. A chi-squared test for trend across the five cases was statistically significant (chi-squared=173.4, 1 df, P<0.0001).

The only statistically significant difference between different grades of anaesthetist was for case 3 (chi-squared=9.92, 2 df, P=0.007). It was noted that this finding was obtained in the context of multiple chi-squared tests.

A number of anaesthetists made comments, revealing a range of conflicting opinions on the management of these patients. Most commented on cut-off values for deferring anaesthesia, with quoted diastolic arterial pressure cut-off values of: 95–100 mm Hg (n=2); 100 mm Hg (n=5); 105 mm Hg (n=4); 110 mm Hg (n=19); 115 mm Hg (n=1); and 120 mm Hg if on antihypertensive medication (n=1). The systolic cut-off values quoted were 160 mm Hg (n=1), 190 mm Hg (n=1), 200 mm Hg if on antihypertensive medication (n=1), and no threshold for systolic arterial pressure. The importance of comorbidity was noted in the comments section.

Comments were also made on the specific management of these patients, with strong and conflicting opinions on the use or avoidance of regional techniques, high dose opiates and intubation. Premedication was recommended by most respondents who made a comment, the majority preferring a beta-blocking agent.

Discussion

A literature search using Medline™ was performed, using the search criteria, 'postal questionnaires' and either 'Anaesthesia' or 'BJA'. This revealed a response rate to postal questionnaires of between 31 and 94%.[15 16] The response rate for this survey was relatively low (52%), although comparable with that reported for other postal surveys of British anaesthetic practice. This low response rate may have introduced bias into our results, if the views of those anaesthetists who responded to the questionnaire are not representative of the study population as a whole. It is certainly possible that the anaesthetists who responded were those with strong views on the peri-operative care of patients with hypertension. However, the wide variation in opinion among the 52% of anaesthetists who did reply is of note and suggests that practice may vary widely. Furthermore, it seems unlikely that the remainder of anaesthetists are absolutely consistent in their views on the management of hypertensive patients. There was no suggestion from our survey of a single consistent view held by a significant minority of anaesthetists. Rather there was a decreasing tendency to postpone surgery as respondents worked their way through the questionnaire, although there was not a trend to decreasing severity of hypertension across the five cases. Only 26% of respondents were prepared to anaesthetize case one. The percentages for the subsequent four cases were 42, 53, 73, and 76%. This trend was statistically significant. It suggests that respondents considered incompletely controlled hypertension to be a cause for concern, but did not have clearly articulated views on what constitutes unacceptable hypertension and did not feel it would be acceptable to cancel all five cases.

The decision to postpone a patient after their admission for surgery has psychological, social, and economic implications, and is not only based on clinical considerations. The overall cancellation rate has been reported at between less than 1 and 27%.[17–20] In a large orthopaedic audit, hypertension was the commonest reason for deferring surgery, accounting for 16.2% of medical cancellations.[17] Another smaller audit found that at orthopaedic preoperative assessment clinic (PAC), 16.7% patients were deferred because of hypertension, accounting for 55.5% of cancellations for medical reasons.[21] While the postponement of an operation in PAC, rather than at admission for surgery, facilitates the efficient use of resources, cancellation within 1–2 weeks of surgery may still cause distress and inconvenience to patients.

It is difficult to defend the wide variations in practice with regard to the management of hypertensive patients presenting for surgery. From the comments made in response to this questionnaire, there seems to be little awareness of either the UK or US hypertension guidelines. The trend in the responses suggests that many anaesthetists feel that hypertension is relevant, but do not have clearly formed views on the appropriate management of these patients.

We offer guidelines below for the peri-operative management of hypertensive patients. These guidelines use the JNCDET V classification of arterial pressure (stage 1, stage 2, etc.). They are consistent with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which recommend deferring anaesthesia if the diastolic pressure is above 110 mm Hg.[22] The ACC/AHA guidelines make no recommendation regarding systolic pressure. There is now clear evidence that systolic arterial pressure is independently associated with target organ damage.[11] We suggest that guidelines for the peri-operative management of hypertensive patients should take into account both systolic and diastolic arterial pressure. Our use of the JNCDET V classification is consistent with this in that it takes into account both systolic and diastolic pressure.[14]

Stage 1 and stage 2 hypertension

Anaesthesia and surgery may proceed in patients with stage 1 and stage 2 hypertension.

Goldman and Caldera were unable to demonstrate an association between poorly controlled hypertension (defined as arterial pressure >160/100 mm Hg) and cardiac complications.[9] A more recent case control study showed no difference in systolic or diastolic pressures between patients who died of a cardiovascular cause within 30 days of anaesthesia and surgery, and controls who did not.[10] The majority of patients in this study had stage 1 or stage 2 hypertension. On the basis of these data there seems little justification for deferring anaesthesia and surgery in patients with stage 1 and stage 2 hypertension.

Stage 3 hypertension

For stage 3 hypertension, it may be wise to be a little more circumspect.

Prys-Roberts and colleagues demonstrated an association between poorly controlled hypertension and the occurrence of intra-operative myocardial ischaemia and arrhythmias.[23] Patients classified as poorly controlled hypertensives in this study had stage 3 or stage 4 hypertension. Another prospective study demonstrated an increasing incidence of post-operative myocardial ischaemia with increasing arterial pressure.[24] On the basis of these findings, we would recommend deferring anaesthesia and surgery in patients with stage 3 hypertension, to allow the arterial pressure to be treated. We would especially recommend this course of action in patients with other cardiovascular risk factors (target organ damage) that may further increase the peri-operative risk.

Stage 4 hypertension

Patients with stage 4 hypertension have severe disease and anaesthesia and surgery should be deferred whenever possible and the arterial pressure treated.

In patients in whom anaesthesia and surgery are deferred, it is clearly important that appropriate anti-hypertensive therapy is started and appropriate follow-up arranged. The most recent UK guidelines recommend use of a thiazide or beta-blocking agent initially.[25] In the elderly, a thiazide is recommended initially. On the basis of studies of peri-operative beta-adrenergic block by Mangano and Poldermans, a beta-blocking agent should probably be the first choice unless contra-indicated.[26 27]

The sequelae of hypertension, such as coronary artery disease and heart failure, appear in a number of risk scoring systems for non-cardiac surgery, including that published recently by Lee and colleagues.[28] Although these conditions may be associated with hypertension, they should be considered as separate risk factors. The ACC/AHA guidelines provide a framework for this.[22] The guidelines assume easy access to non-invasive cardiac testing, coronary angiography and coronary revascularisation before surgery, and may be difficult to apply in settings where these resources are limited. However, the guidelines can be modified for local use, and would help to ensure optimal medical treatment.

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References

1 Maggio C, Bonzano A, Conte E, et *al.* Preoperative evaluation in non-cardiac surgery. *Qual Assur Health Care* 1992; **4**: 217–24

2 Leslie JB. Incidence and aetiology of preoperative hypertension. *Acta Anaesthesiol Scand* 1993; **37** (Suppl 99): S5–9

3 Wolfsthal SD. Is blood pressure control necessary before surgery? *Med Clin North Am* 1993; **77**: 349–62

4 Nahar T, Devereux RB. Hypertension, cardiac hypertrophy and the effects of anaesthesia. In: *Baillière's Clinical Anaesthesiology.* London: Baillière Tindall, 1997; **11**: 675–703

5 Howell SJ, Sear YM, Yeates D, Goldacre M, Sear JW, Foëx P. Risk factors for cardiovascular death after elective surgery under general anaesthesia. *Br J Anaesth* 1998; **80**: 14–9

6 Allman KG, Muir A, Howell SJ, Hemming AE, Sear JW, Foëx P. Resistant hypertension and preoperative silent myocardial ischaemia in surgical patients. *Br J Anaesth* 1994; **73**: 574–8

7 Raby KE, Barry J, Creager MA, et *al.* Detection and significance of intra-operative and postoperative myocardial ischaemia in peripheral vascular surgery. *JAMA* 1992; **268**: 222–7

8 Mangano DT, Browner WS, Hollenberg M, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. *JAMA* 1992; **268**: 233–9

9 Goldman L, Caldera DL. Risks of general anesthesia and elective surgery in the hypertensive patient. *Anesthesiology* 1979; **50**: 285–92

10 Howell SJ, Sear YM, Yeates D, Goldacre M, Sear JW, Foëx P. Hypertension, admission blood pressure and peri-operative cardiovascular risk. *Anaesthesia* 1996; **51**: 1000–4

11 Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993; **153**: 598–615

12 Staessen J, Fagard R, Amery A. Isolated systolic hypertension in the elderly: implications of Systolic Hypertension in the Elderly Program (SHEP) for clinical practice and for the ongoing trials. *J Hum Hypertens* 1991; **5**: 469–74

13 O'Malley K, Cox JP, O'Brien E. Further learnings from the European Working Party on High Blood Pressure in the Elderly (EWPHE) study: focus on systolic hypertension. *Cardiovasc Drugs Ther* 1991; **4** (Suppl 6): S1249–51

14 The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1993; **153**: 154–83

15 Stoddart PA, Brennan L, Hatch DJ, Bingham R. Postal survey of paediatric practice and training among consultant anaesthetists in the UK. *Br J Anaesth* 1994; **73**: 559–63

16 Knowles PR, Bryden DC, Kishen R, Gwinnutt CL. Meeting the standards for interhospital transfer of adults with severe head injury in the United Kingdom. *Anaesthesia* 1999; **54**: 283–8

17 Wildner M, Bulstrode C, Spivey J, Carr A, Nugent I. Avoidable causes of cancellation in elective orthopaedic surgery. *Health Trends* 1991; **23**: 115–6

18 Tait AR, Voepel-Lewis T, Munro HM, Gutstein HB, Reynolds PI. Cancellation of pediatric outpatient surgery: economic and emotional implications for patients and their families. *J Clin Anesth* 1997; **9**: 213–9

19 Morrisey S, Alun-Jones T, Leighton S. Why are operations cancelled? *BMJ* 1989; **299**: 77

20 Starsnic MA, Guarnieri DM, Norris MC. Efficacy and financial benefit of an anesthesiologist-directed university preadmission evaluation center. *J Clin Anesth* 1997; **9**: 299–305

21 West R, Galasko CSB. Medical audit: the role of an orthopaedic preoperative clinic. *Ann R Coll Surg Engl* 1995; **77** (Suppl): 134–5

22 Eagle KA, Brundage B, Chaitman BR, et *al.* ACC/AHA Task Force Report. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. *Circulation* 1996; **93**: 1278–317

23 Prys-Roberts C, Meloche R, Foëx P. Studies of anaesthesia in relationship to hypertension. I: Cardiovascular responses of treated and untreated patients. *Br J Anaesth* 1971; **43**: 122–37

24 Howell SJ, Hemming AE, Allman KG, Glover L, Sear JW, Foëx P. Predictors of postoperative myocardial ischaemia. *Anaesthesia* 1997; **52**: 107–11

25 Ramsay LE, Williams B, Johnston GD, et *al.* British Hypertension Society guidelines for hypertension management 1999: summary. *BMJ* 1999; **319**: 630–5

26 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after non cardiac surgery. *N Engl J Med* 1996; **335**: 1713–20

27 Poldermans D, Boersma E, Bax JJ, et *al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high risk patients undergoing vascular surgery. *N Engl J Med* 1999; **341**: 1789–94

28 Lee TH, Marcantonio ER, Mangione CM, et *al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9

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Oesophageal Doppler monitoring overestimates cardiac output during lumbar epidural anaesthesia

H. A. Leather and P. F. Wouters*

Department of Anaesthesiology, University Hospitals, Katholieke Universiteit Leuven, U. Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

**Corresponding author*

Oesophageal Doppler monitoring (ODM) has been advocated as a non-invasive means of measuring cardiac output (CO). However, its reliance upon blood flow measurement in the descending aorta to estimate CO is susceptible to error if blood flow is redistributed between the upper and lower body. We hypothesize that lumbar epidural anesthesia (LEA), which causes blood flow redistribution, causes errors in CO estimates. We compared ODM with thermodilution (TD) measurements in fourteen patients under general anaesthesia for radical prostatectomy, who had received an epidural catheter at the intervertebral level L2–L3. Coupled measurements of CO by means of the TD and ODM techniques were performed at baseline (general anaesthetic only) and after epidural administration of 10 ml of 0.25% bupivacaine. The two methods were compared using Bland-Altman analysis: before LEA there was a bias of –0.89 litre min^{-1} with limits of agreement ranging between –2.67 and +0.88 litre min^{-1}. Following lumbar sympathetic block, bias became positive (+0.55 litre min^{-1}) and limits of agreement increased to –3.21 and +4.30 litre min^{-1}. ODM measured a greater increase in CO after LEA (Δ=+1.71 (1.19) litre min^{-1} (mean (SD)) compared with TD (Δ=+0.51 (0.70) litre min^{-1}). We conclude that following LEA, measurements with the Oesophageal Doppler Monitor II overestimate CO and show unacceptably high variability. Blood flow redistribution may limit the value of ODM.

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Keywords: measurement techniques, cardiac output; measurement techniques, oesophageal Doppler; anaesthetic techniques, epidural

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The accuracy of oesophageal Doppler monitoring (ODM)[1] of cardiac output (CO) is controversial. Some authors have claimed it to be at least as accurate as thermodilution (TD).[2 3] Others have shown that ODM is less accurate than the TD technique, which is the standard clinical method.[4 5] The developers of commercially available ODM equipment agree that it gives less accurate absolute measurements than TD, and that the clinician using it should concentrate on trends in CO rather than absolute values.[6] Several of the validation publications of the ODM machines show bias plots of relative change but not absolute values.[7–9] Theoretically, ODM should be a relatively non-invasive, cheap and easy means of measuring CO. The technique is easier to master, less expensive and less invasive than the use of a TD catheter, but, training is required to best use the ODM technique.[10 11] Variations in cross-sectional area of the descending aorta and the angle between the probe and the descending aorta may not be taken into account.[12 13]

The ODM II machine (Abbot Laboratories, North Chicago, IL, USA) uses a nomogram to estimate CO from Doppler flow measurements in the descending aorta. To calculate CO, the oesophageal Doppler machine has to take into account the blood flow that it does not measure (i.e. flow to the upper body), and assumes that 30% of CO goes to the upper body. Variations in blood flow distribution may, therefore, lead to errors in CO estimates. Situations involving blood flow redistribution where ODM is inaccurate include haemorrhage[13 14] and aortic cross-clamping.[12] Lumbar epidural anaesthesia (LEA) increases blood flow to the lower body by sympathetic nerve block, and reduces flow to the upper body by compensatory vasoconstriction caused by increased sympathetic nerve activity.[15–19] The ODM II machine could overestimate CO in these circumstances.

We measured the accuracy of CO estimation using ODM during LEA as an example of a clinical setting involving

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Table 1 Haemodynamic data before and after LEA. ABPs, d, m=systolic, diastolic and mean arterial pressure, CVP=central venous pressure, MPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, HR=heart rate. Data are mean (SD) [range]. Pressures are in mm Hg, heart rate is in beats min^{-1}. *=$P<0.05$ *vs* control. Data displayed post-epidural are obtained from the measurement coinciding with peak CO as measured with TD

	Baseline	Post-epidural
ABPs	104 (17) [88–144]	90* (15) [74–115]
ABPd	58 (10) [43–74]	49* (8) [39–61]
ABPm	74 (12) [61–97]	63* (10) [50–79]
CVP	11 (3) [6–17]	10* (4) [4–17]
MPAP	21 (4) [14–28]	21 (5) [14–27]
PCWP	14 (3) [7–17]	13 (3) [8–19]
HR	62 (10) [51–80]	66 (12) [52–88]

redistribution of blood flow between the upper and lower body.

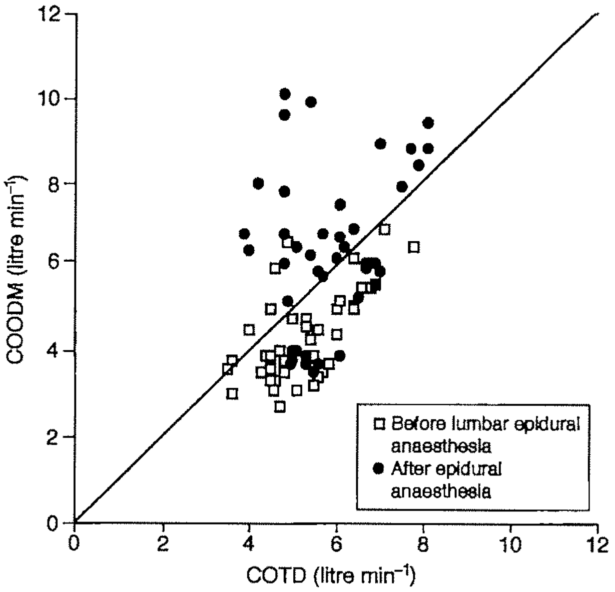

Fig 1 Scattergram of CO measurements by ODM *vs* TD before and after LEA. COODM=CO value obtained by ODM; COTD=CO value obtained by TD.

Methods

The study was approved by the ethical committee of the University Hospitals of the Katholieke Universiteit Leuven. Informed consent was obtained from participating patients.

Fourteen male patients (mean age 65 yr (range 58–73), mean weight 80 kg (range 61–110), mean height 176 cm (range 172–184), ASA class I or II), all undergoing radical prostatectomy under general anaesthesia, were included in the study. A history of severe cardiac disease, respiratory or oesophageal pathology were exclusion criteria. The oesophageal Doppler monitor used for this study (ODM II) emits a continuous 4 MHz ultrasound signal, which is received through a 300 Hz high-pass filter. The blood flow velocity curve is displayed continuously and an on-line display of CO, heart rate and stroke volume is provided.

For the purpose of intra- and post-operative analgesia, a lumbar epidural catheter was inserted at the level of intervertebral space L2–L3 before induction of anaesthesia. Anaesthesia was induced with propofol 1.5–2 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} and sufentanil 0.2–0.3 µg kg^{-1}, and maintained by means of isoflurane 1.2–1.5 MAC and 65% nitrous oxide with supplemental sufentanil. Following orotracheal intubation, the lungs were mechanically ventilated with a mixture of 35% oxygen and nitrous oxide. A 20-gauge catheter was inserted in the radial artery and a TD catheter was introduced via the right internal jugular vein.

The oesophageal probe was inserted in the standard manner by experienced personnel; optimal positioning was obtained from the appearance and sound of the Doppler signal. Patient age and weight were entered into the ODM console nomogram.

Coupled measurements of CO by TD (triplicate measurements with ice-cold saline) and ODM techniques were performed three times at fixed intervals during the general anaesthetic and then 20, 25 and 30 min after injection of 10 ml bupivacaine 0.25%. Arterial pressure, pulmonary artery pressure, central venous pressure and pulmonary capillary wedge pressure were recorded immediately after each CO determination. An i.v. infusion of 500 ml of a colloid solution (Geloplasma®) was then administered over 30 min in order to prevent severe arterial hypotension.

CO measurements with ODM and TD were compared using Bland-Altman analysis.[20] Paired *t*-tests were used to test the significance of changes in haemodynamic parameters after epidural anaesthesia. A probability of less than 0.05 was considered statistically significant to reject the null hypothesis.

Results

Upon awakening, all patients were free of pain and had loss of temperature sensation in the corresponding dermatomes.

The epidural anaesthesia reduced arterial pressure (mean arterial pressure from (mean (SD) 74 (12) (range 61–97) to 63 (10) (range 50–79) mm Hg) and central venous filling pressure (from 11 (3) (range 6–17) to 10 (4) (range 4–17) mm Hg) as measured at the moment of peak CO (TD method). Heart rate, pulmonary artery pressure and pulmonary capillary wedge pressure did not change (Table 1).

Measurements after LEA remained stable over the 10-min observation period (no significant difference between variables obtained 20 and 30 min after the onset of LEA respectively; paired *t*-test).

Before LEA, TD and ODM techniques showed acceptable agreement (mean difference −0.89 litre min^{-1}, limits of agreement −2.67 and +0.88 litre min^{-1}; SE of the mean difference=0.95, SE of the limits of agreement=0.23 (Figs 1 and 2A)). Both ODM and TD CO increased after LEA. However, the increase measured by ODM (from 4.84 (1.26)

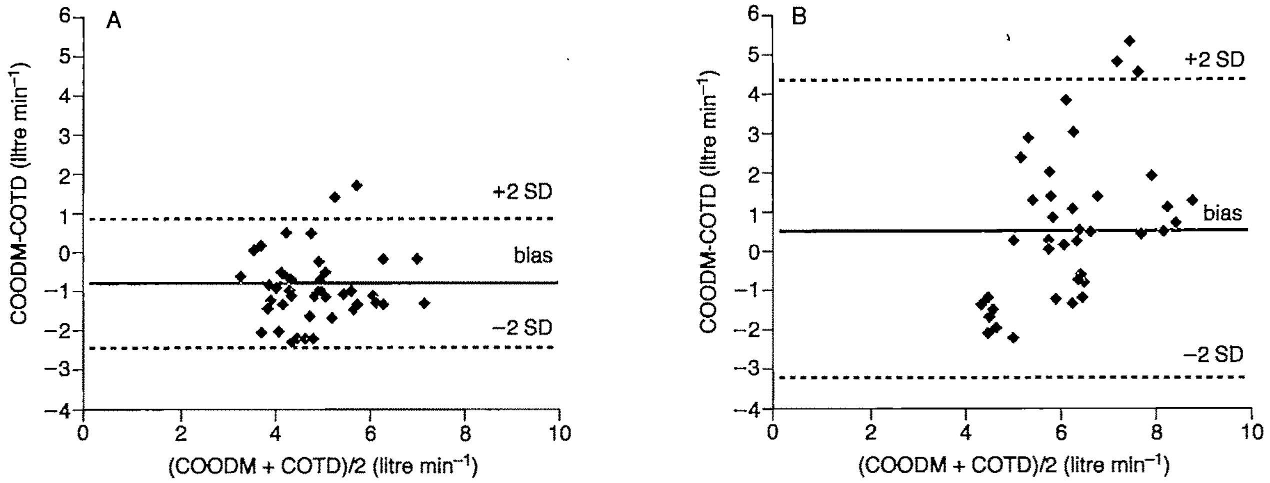

Fig 2 Bias plot of CO measurements by ODM *vs* TD before (A) and after (B) LEA.

to 6.54 (1.99) litre min^{-1}; Δ=+1.71 (1.19) litre min^{-1}) was greater than that measured using the TD technique (from 5.60 (1.16) to 6.11 (1.10) litre min^{-1}; Δ=+0.51 (0.70) litre min^{-1}; $P<0.05$). During LEA, in contrast to baseline circumstances, ODM overestimated CO (mean difference +0.55 litre min^{-1}, SE of the mean difference=0.29) and displayed unacceptably wide limits of agreement (limits of agreement −3.21 and +4.30 litre min^{-1}, SE of the limits of agreement=0.50) (Figs 1 and 2B).

Discussion

We observed an acceptable agreement between ODM and TD in baseline conditions, with a negative bias. This slight underestimation of CO by ODM has been reported previously[4 12] but not consistently.[3 5 10] Compared with several other studies, we found similar limits of agreement.[3–5 10 12]

LEA increased CO as measured by both TD and ODM, explained by a reduction in systemic vascular resistance and maintenance of an adequate preload by volume infusion.[21]

The main result of this study is that ODM overestimates CO during LEA. There is no theoretical reason to believe that lack of agreement between ODM and TD measurements during epidural anaesthesia should be caused by an underestimation of CO by TD. LEA causes blood pooling in the capacitance vessels of the lower limbs,[16] but this should not affect the accuracy of the TD method which measures blood flow in the pulmonary circulation.

Movement artefacts are unlikely to cause error considering the type of surgery involved. Variation in cross-sectional area of the aorta has been suggested as an important potential cause of inaccuracy of ODM.[12 13] Considering our patient characteristics, errors caused by aortic compliance are unlikely. A decrease in area of the descending aorta could theoretically overestimate CO. The decrease in arterial pressure which we observed could have caused a small decrease in aortic area, but it is very unlikely that it should have caused a 4-fold decrease needed if this were to be the sole cause of error.

Overestimation by ODM is probably caused by the redistribution of blood to the lower body, at the expense of the upper body segment. The fixed distribution assumed by the ODM II suggests that the machine cannot compensate for such variations in blood flow distribution. ODM has been found inaccurate in haemorrhage[13 14] and aortic cross-clamping where redistribution is likely. Klotz and co-workers observed an increase in bias between TD and ODM from −0.96 to −1.51 litre min^{-1} during aortic cross-clamping in six patients.[12] Underestimation of CO by ODM during aortic cross-clamping can be explained by blood flow redistribution from the lower to the upper body.

The new generation of ODM devices (such as the Hemosonic 100, Arrow[22]) measure aortic diameter. Although this may assess any possible inaccuracy of ODM caused by variations in aortic CSA, it will not solve the problem of blood flow redistribution between the upper and lower body.

We propose that the blood flow redistribution in circumstances like LEA, aortic cross-clamping, haemorrhagic and distributive shock can partially explain the inaccuracy of ODM CO measurements, and caution is necessary when using ODM to estimate CO.

References

1 Side CD, Gosling RJ. Non-surgical assessment of cardiac function. *Nature* 1971; **232**: 335–6

2 Madan AK, UyBarreta VV, Aliabadi-Wahle S, *et al.* Esophageal Doppler ultrasound monitor versus pulmonary artery catheter in the hemodynamic management of critically ill surgical patients. *J Trauma* 1999; **46**: 607–12

3 Valtier B, Cholley BP, Belot JP, de la Coussaye JE, Mateo J, Payen DM. Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. *Am J Respir Crit Care Med* 1998; **158**: 77–83

4 Schmid ER, Spahn DR, Tornic M. Reliability of a new generation

transesophageal Doppler device for cardiac output monitoring. *Anesth Analg* 1993; **77**: 971–9

5 Keyl C, Rödig G, Lemberger P, Hobbhahn J. A comparison of the use of transoesophageal Doppler and thermodilution techniques for cardiac output determination. *Eur J Anaesthesiol* 1996; **13**: 136–42

6 Singer M. Esophageal Doppler monitoring of aortic blood flow: beat-by-beat cardiac output monitoring. *Int Anesthesiol Clin* 1993; **31**: 99–125

7 Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. *Crit Care Med* 1991; **19**: 1132–7

8 Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Crit Care Med* 1989; **17**: 447–52

9 Singer M, Bennett D. Optimisation of positive end expiratory pressure for maximal delivery of oxygen to tissues using oesophageal Doppler ultrasonography. *BMJ* 1989; **298**: 1350–3

10 Lefrant JY, Bruelle P, Aya AGM, *et al.* Training is required to improve the reliability of esophageal Doppler to measure cardiac output in critically ill patients. *Intensive Care Med* 1998; **24**: 347–52

11 Krishnamurthy B, McMurray TJ, McClean E. The peri-operative use of the oesophageal Doppler monitor in patients undergoing coronary artery revascularisation. A comparison with the continuous cardiac output monitor. *Anaesthesia* 1997; **52**: 624–9

12 Klotz KF, Klingsiek S, Singer M, *et al.* Continuous measurement of cardiac output during aortic cross-clamping by the oesophageal Doppler monitor ODM I. *Br J Anaesth* 1995; **74**: 655–60

13 Wong DH, Watson T, Gordon I, *et al.* Comparison of changes in transit time ultrasound, esophageal Doppler, and thermodilution cardiac output after changes in preload, afterload, and contractility in pigs. *Anesth Analg* 1991; **72**: 584–8

14 Kamal GD, Symreng T, Starr J. Inconsistent esophageal Doppler cardiac output during acute blood loss. *Anesthesiology* 1990; **72**: 95–9

15 Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. *Anesthesiology* 1986; **65**: 139–43

16 Arndt JO, Höck A, Stanton-Hicks M, Stühmeier K.-D. Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–23

17 Taniguchi M, Kasaba T, Takasaki M. Epidural anesthesia enhances sympathetic nerve activity in the unanesthetized segments in cats. *Anesth Analg* 1997; 84: 391–7

18 Hopf HB, Weissbach B, Peters J. High thoracic segmental epidural anesthesia diminishes sympathetic outflow to the legs, despite restriction of sensory blockade to the upper thorax. *Anesthesiology* 1990; **73**: 882–9

19 Hickey NC, Wilkes MP, Howes D, Watt J, Shearman CP. The effect of epidural anaesthesia on peripheral resistance and graft flow following femorodistal reconstruction. *Eur J Vasc Endovasc Surg* 1995; **9**: 93–6

20 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–10

21 Wright PMC, Fee JPH. Cardiovascular support during combined extradural and general anaesthesia. *Br J Anaesth* 1992; **68**: 585–9

22 Cariou A, Monchi M, Joly LM, *et al.* Noninvasive cardiac output monitoring by aortic blood flow determination: evaluation of the Sometec Dynemo-3000 system. *Crit Care Med* 1998; **26**: 2066–72

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The lumbar epidural space in pregnancy: visualization by ultrasonography

T. Grau*, R. W. Leipold, J. Horter, R. Conradi, E. Martin and J. Motsch

Department of Anaesthesiology, University of Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany

**Corresponding author*

Epidural anaesthesia is an important analgesia technique for obstetric delivery. During pregnancy, however, obesity and oedema frequently obscure anatomical landmarks. Using ultrasonography, we investigated the influence of these changes on spinal and epidural anatomy. We examined 53 pregnant women who were to receive epidural block for vaginal delivery or Caesarean section. The first ultrasound imaging was performed immediately before epidural puncture; the follow-up scan was done 9 months later. The ultrasound scan of the spinal column was performed at the L3/4 interspace in transverse and longitudinal planes, using a Sonoace 6000 ultrasonograph (Kretz®, Marl, Germany) equipped with a 5.0-MHz curved array probe. We measured two distances from the skin to the epidural space: the minimum (perpendicular) and the maximum (oblique) needle trajectory. The quality of ultrasonic depiction was analysed by a numerical scoring system. An average weight reduction of 12.5 kg had occurred by the follow-up examination. During pregnancy, the optimum puncture site available on the skin for epidural space cannulation was smaller, the soft-tissue channel between the spinal processes was narrower, and the skin–epidural space distance was greater. The epidural space was narrower and deformed by the tissue changes. The visibility of the ligamentum flavum, of the dura mater and of the epidural space decreased significantly during pregnancy. Nevertheless, ultrasonography offered useful pre-puncture information. Thus far, palpation has been the only available technique to facilitate epidural puncture. Ultrasound imaging enabled us to assess the structures to be perforated. We anticipate that this technique will become valuable clinically.

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Since Pages[1] took the first steps to introducing epidural block over 80 yr ago, the technique of epidural anaesthesia has steadily been improved upon. Major advances have been achieved in needle design and drug combinations, but identifying the epidural space still relies solely on a loss of resistance technique. Nevertheless, the accurate identification of the epidural space is the most vital part of the technique. For epidural block, correctly identifying the location of the space not only determines the success or failure of the epidural space procedure,[2] but may also influence the onset of action and rate of absorption of the drugs.[3]

Ultrasound imaging is widely used in medicine, but identification of the epidural space by ultrasonography is hampered by the surrounding bony structures.[4] The great improvement in ultrasound technology in recent years has increased the possibility of it becoming a valuable tool before the performance of neuraxial anaesthesia. The first successful studies in the field of ultrasonic measurement of the epidural space date back 20 yr, when Cork and colleagues[5] and Currie[6] observed a strong relationship between the epidural space depth seen on ultrasonic images and the distance to the point of the epidural needle. Wallace[7] confirmed that needle depth is predictable from ultrasound depth measurement. In a more recent study, Bonazzi and de Gracia[8] were the first to identify the lumbar ligamentum flavum. They established the usefulness of ultrasound examination before epidural space puncture.

However, detailed knowledge of the pregnancy-related variability of the anatomy of the lumbar spinal column and its flanking ligaments is not available. In our clinic, parturients often present with abnormal anatomical condi-

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tions such as scoliosis, hyperlordosis or kyphosis of the lumbar spine, severe obesity or local oedema, which can obscure anatomical landmarks. Additionally, hormonal changes during pregnancy result in an alteration in tissue consistency. Collagen concentration and organization, relative molecular proportions and the water content of the tissue are altered.[9] [10] Subsequently, the structure of the interspinous ligament becomes softer and inhomogeneous. This often causes false loss of resistance, which can lead to malplacement of the epidural catheter.

Our aim was to investigate the influence of the tissue alterations of pregnancy on epidural technique. We scanned the lumbar epidural space of women during and after pregnancy. Variability in size of the L3/4 intervertebral space and changes in the localization of the ligamentum flavum and dura mater were recorded. We also graded how well the main anatomical landmarks were visualized by ultrasonography.

Materials and methods

The ethics committee of Heidelberg University granted approval for this prospective follow-up study. We used a standardized study procedure, and written informed consent was obtained from all of the participating parturients, whose age, height, weight, and ASA index were noted. We examined 60 pregnant women who had been admitted to the university clinic to give birth and were to receive epidural block for vaginal delivery or Caesarean section. The first examination was performed immediately before epidural puncture and childbirth; the follow-up scan was done after a 250–300-day period.

Parturients who did not require epidural anaesthesia or in whom it was impossible for medical reasons were excluded from the study, as were obstetric emergencies. None of the patients had a history of spinal surgery or trauma, or evidence of congenital spinal abnormalities. In a short clinical examination, we looked for signs of scoliosis, kyphosis or hyperlordosis, and local oedema (Table 1). The time taken for ultrasonic measurement was noted.

The scan of the spinal column was performed at the L3/4 interspace with the patient in the sitting position. The different transmission velocities of the ultrasonic beam through soft tissue and bone causes intense reflection and refraction at the soft tissue/bone interfaces.[11] A high percentage of ultrasound energy in epidural scans is lost on bone structures, which causes acoustic shadows on the resulting image. Each spinal process accounts for one shadow and the adjacent intervertebral space for one acoustic window. We performed scans in transverse and longitudinal planes. A Sonoace 6000 ultrasonograph (Kretz®, Marl, Germany) equipped with a 5.0-MHz curved array probe was used. Angles and distances were measured (mm) by the built-in software.

The needle length for epidural space puncture is shortest when the needle is advanced perpendicularly to the skin surface. This distance was measured in the transverse scanning plane. The distance is longest in a maximal oblique trajectory, which is the path along the spinal process. This distance was assessed in the longitudinal scanning plane. We also measured the angle between these trajectories.

The quality of ultrasonic depiction of the epidural space and the surrounding landmarks was analysed by a numeric scoring system (Table 2). The extent of the acoustic shadows was evaluated similarly (Table 2). In both scanning planes, the diameter of the intrathecal space (i.e. the distance between ligamentum flavum and vertebral body)

Table 1 Physical characteristics of patients and pregnancy-related alterations. Data are mean (SD) [range]

	Pregnant	Not pregnant	Significance
Age (yr)	32.3 (4.4) [20–40]	33.0 (4.4) [21–41]	
Weight (kg)	81.0 (19.1)	68.5 (20.2)	$P<0.001$
Height (cm)	166.5 (7.5)	166.6 (7.4)	n.s.
Body Mass Index (kg m^{-2})	29.2 (6.5)	24.7 (7.1)	$P<0.001$
Dubois Index (cm^2)	21057.1 (2500.0)	19472.9 (2634.6)	$P<0.001$
ASA Index (median)	2	2	n.s.
Pregnancy duration (days)	269 (16.4)		
Time passed to second scan (days)		272 (8.5)	

Table 2 Synopsis of the scales of evaluation. All findings from the physical examination were numerically scored (0–3). The visibility of landmarks and the effect of acoustic shadows on the picture quality in the ultrasound examination, were evaluated in the same way

		0	1	2	3
Deviation from the longitudinal axis	*sagittal*	none	<2 cm	2–4 cm	>4 cm
	lateral	none	<2 cm	2–4 cm	>4 cm
Oedema		none	slight	moderate	severe
Ultrasonic visibility	*detectable*	not	hardly	well	very well
Acoustic shadow		none	small	intermediate	no ultrasound penetration

Table 3 The number of patients with lumbar scoliosis, kyphosis, hyperlordosis and oedema during and after the pregnancy. For explanation of the scaling see Table 2

	Scoliosis		**Kyphosis**		**Lordosis**		**Oedema**	
P=pregnant, N=not pregnant	P	N	P	N	P	N	P	N
Degree [0]	42	43	45	46	49	49	39	44
Degree [1]	2	5	6	6	2	4	6	8
Degree [2]	6	5	2	1	2	0	7	1
Degree [3]	3	0	0	0	0	0	1	0
Significance	*P*<0.29 (n.s.)		*P*<0.84 (n.s.)		*P*<0.26 (n.s.)		*P*<0.14 (n.s.)	

Table 4 Visibility of the key structures and influence of the acoustic shadows on the picture quality during and after pregnancy. For explanation of the scaling see Table 2

		Pregnant	**Not pregnant**	**Significance**
Visibility	Spinous process	1.5 (0.5)	1.7 (0.5)	n.s.
	Interarticular process	2.0 (0.7)	2.5 (0.6)	*P*<0.001
	Costal process	2.6 (0.5)	2.7 (0.5)	n.s.
	Ligamentum flavum	2.7 (0.5)	2.9 (0.3)	*P*<0.005
	Epidural space	1.4 (0.5)	1.7 (0.5)	*P*<0.004
	Dura mater	1.0 (0.4)	1.4 (0.5)	*P*<0.001
	Intrathecal region	0.9 (0.4)	1.0 (0.3)	n.s.
	Vertebral bodies	2.2 (0.6)	2.8 (0.4)	*P*<0.008
	Vertebral disks	0.1 (0.3)	0.3 (0.5)	n.s.
Acoustic shadow effects	Spinous process	1.1 (0.8)	0.9 (0.6)	n.s.
	Interarticular process	1.2 (0.7)	1.1 (0.8)	n.s.
	Costal process	1.3 (0.6)	1.5 (0.6)	n.s.
	Vertebral bodies	1.7 (0.7)	2.1 (0.5)	n.s.

was measured. We assessed the visible part of the ligamentum flavum between the vertebral arches (longitudinal extent) as the size of the 'target area'.

Follow-up scan was performed 250–300 days after the first examination. A total of 53 patients (88.3%) presented for re-examination. Once again, sonotopography of the epidural structures was performed as described above.

Statistics

We recorded all data on standardized forms using tick boxes. Data were analysed using the chi-squared test with Yates correction where appropriate, or using Student's *t*-test. Excel 97™ Microsoft™, SPSS 7.5™ and Primer Biostatistik 4.04™ (S. A. Glantz) software were used for statistical analysis. Data are given as mean (SD) unless stated otherwise.

Results

From the 60 parturients participating in the study, 53 women presented for follow-up examination. Only their data were evaluated. There were no premature births in this group. All ultrasound scans were performed in the 38th week of pregnancy or later. On average, the follow-up scan was performed 272 days after childbirth. At this time, no participant was pregnant. The physical characteristics of the patients and changes in body indices are listed in Table 1. The first ultrasonic examination and documentation took 8.4 (4.1) min, so that analgesia onset time was not substantially delayed by participating in the study.

At the first clinical examination, 11 patients (20.8%) presented with axis deviation of the spine and 14 (26.4%) showed lumbar oedema. One parturient suffered from pre-eclampsia and presented with severe oedema. The number of pathological findings decreased at the follow-up examination, but no significant difference could be established (Table 3).

In the first examination, the visibility of the ligamentum flavum, the major target of epidural space ultrasonography, was scored as 'very well detectable' (2.7 (0.5); for all numerical scoring see Table 2). The visibility of the epidural space was scored as relatively poor (1.4 (0.5)) (Fig. 1), and the visibility of the dura mater (1.0 (0.4)) and intrathecal space (0.9 (0.4)) (Fig. 2).

The vertebral body in the pregnancy state caused a strong signal on ultrasound images (2.2 (0.6)), whereas the vertebral discs could hardly be demonstrated at all (0.1 (0.3)). The visibility of the spinous process was rated as 1.5 (0.5) (Table 4). Figure 3 shows the typical findings.

The follow-up examination 9 months post-partum showed noticeable improvements in visibility. The liga-

Table 5 Comparison of ultrasonic measurements during and after pregnancy. The minimal distance was measured perpendicularly, the maximal distance in an oblique trajectory along the spinal process. The angles given were measured between the diagonal and the perpendicular trajectory. The height of the flaval ligament corresponds to the size of the target area. *'distance'=distance between skin surface and lig. flavum

Measured values	Trajectory	Units	Pregnant	Not pregnant	Significance
Minimum distance*	Horizontal	(mm)	49.5 (8.1)	44.6 (7.3)	*P*<0.001
Maximum distance*	Diagonal	(mm)	53.6 (8.5)	48.3 (7.3)	*P*<0.001
Puncture angle	Diagonal	(degree)	17.5 (2.5)	19.8 (3.7)	*P*<0.001
Height of lig. flavum		(mm)	9.1 (1.4)	8.7 (1.0)	n.s.
Diameter of the intervertebral space		(mm)	10.7 (1.7)	11.6 (1.6)	*P*<0.006

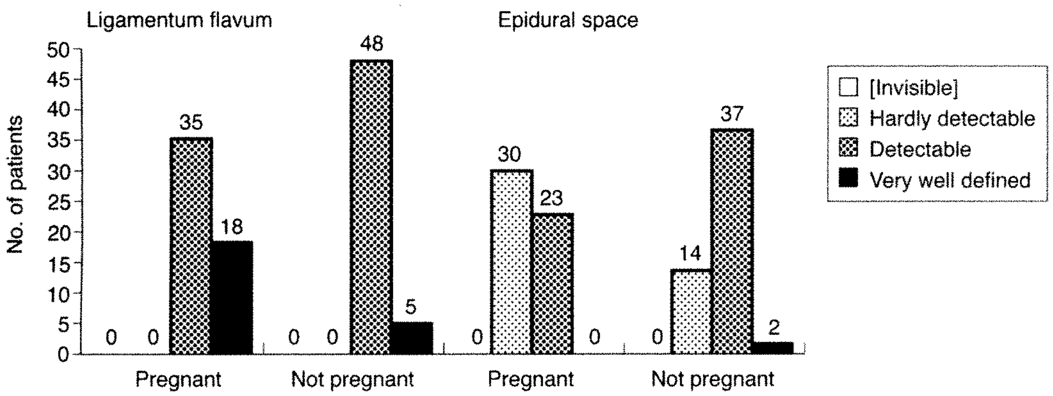

Fig 1 Comparison of the visibility of the ligamentum flavum and the epidural space in pregnant and non-pregnant patients (*P*<0.01).

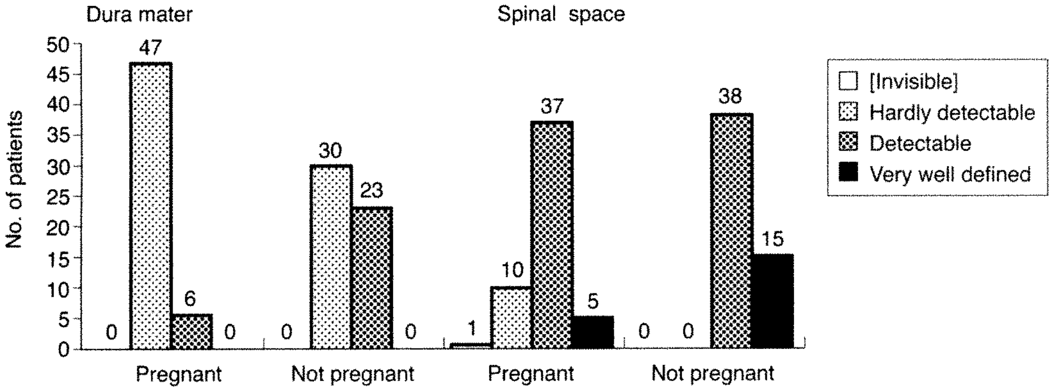

Fig 2 Comparison of the visibility of the dura mater and of the spinal space in pregnant and non-pregnant patients (*P*<0.001).

mentum flavum could easily be recognized (mean score of 2.9 (0.3); *P*<0.005). The epidural space itself (1.7 (0.5); *P*<0.004) and the dura mater (1.4 (0.5); *P*<0.001) were identified without difficulty more frequently.

Figures 1 and 2 indicate that the ligamentum flavum was detectable by ultrasound in both the pregnant and non-pregnant states. But the epidural space was hardly detectable in 57% of pregnant patients yet was detectable in 75% of those who were not pregnant (Fig. 1). The dura was hardly detectable in 88% of the pregnant and 56% of the non-pregnant group (Fig. 2).

The visibility of the intrathecal space post-partum was rated as 1.0 (0.3; n.s.) (Table 4). The visibility of the vertebral body was significantly better (2.8 (0.4); *P*<0.008), and the visibility of the spinous process was 1.7 (0.5; n.s.). As in pregnancy, the vertebral discs could not be detected satisfactorily (0.3 (0.5)). The intensity of the acoustic shadows showed no significant alteration post-partum (Table 4). Figure 4 shows typical findings.

During pregnancy, the average length of the perpendicular trajectory from the skin surface to the ligamentum flavum was 49.5 (8.1) mm. The maximum distance was 53.6 (8.5) mm with an angle of 17.5 (2.5)° to the horizontal trajectory. The height of the spinal interspace was 10.7 (1.7) mm (Table 5).

In the follow-up examination, the minimum distance from the skin to the flaval ligament was reduced to 44.6 (7.3) mm (*P*<0.001). The angle along the spinous process

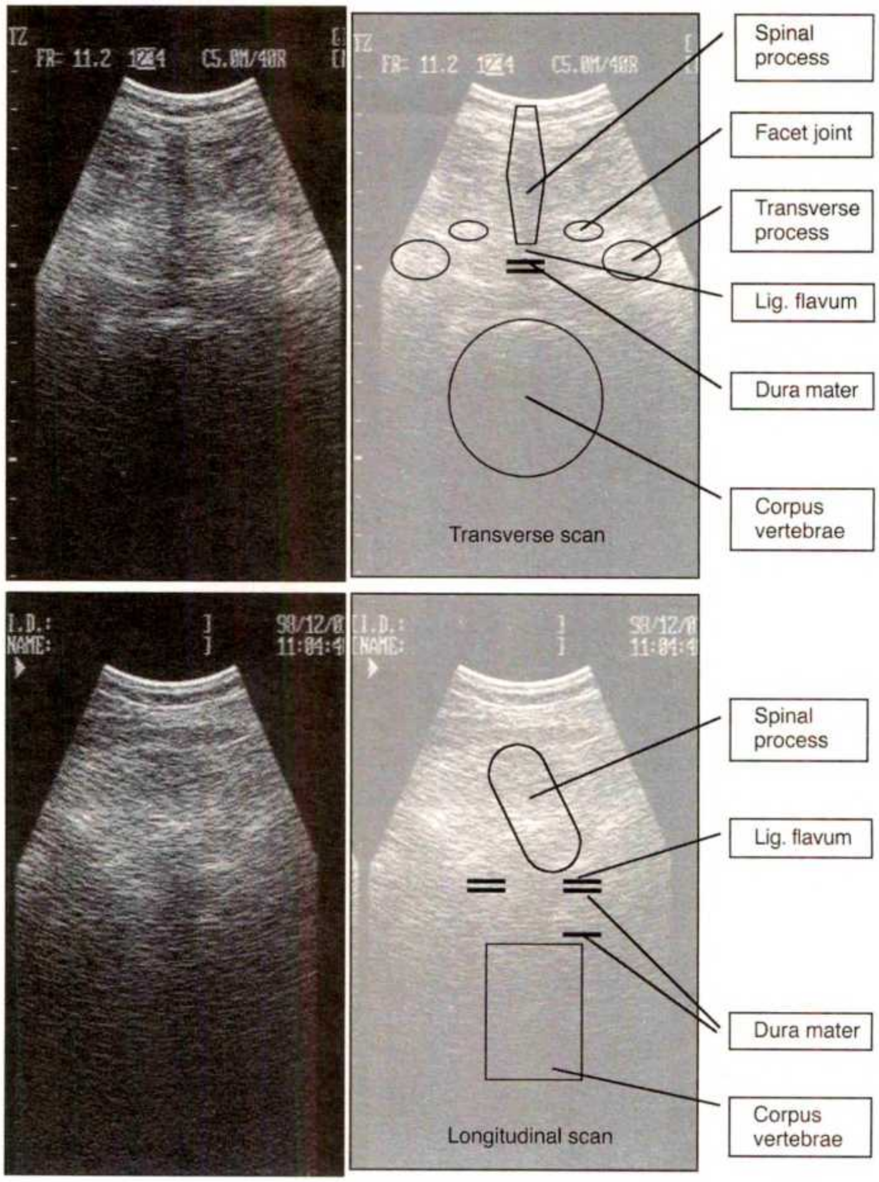

Fig 3 Perperndicular ultrasound scans of a pregnant patient transected longitudinally with an additional graphic for the explanation of the localization.

was wider (19.8 (3.7)°; $P<0.001$) and the maximum distance was smaller (48.3 (7.3) mm; $P<0.001$). The height of the spinal interspace increased significantly to 11.6 (1.6) mm ($P<0.006$) (Table 4).

Discussion

Even under normal anatomical conditions, the performance of neuraxial regional anaesthesia is technically demanding. It has been recommended that it should only be performed by experienced practitioners after adequate training.[12] The importance of a meticulous technique for the avoidance of complications has been emphasized repeatedly.[13 14] During pregnancy, obesity and oedema frequently obscure anatomical landmarks,[7] the interspinal ligament is hormonally softened, and inhomogeneous tissue can cause false loss of resistance. These changes may make neuraxial anaesthesia technically more difficult with more complications.

In this study, pregnancy-associated weight gain and tissue changes resulted in significant changes in spinal anatomy. These alterations were readily observed by the use of ultrasound imaging. During pregnancy, the epidural space was located deeper under the skin surface in all patients. The upward gradient of the space between the spinal processes was steeper and, hence, so was the angle of epidural space puncture. The size of the ligamentum flavum 'target area' did not seem to alter yet the diameter of the L3/4 intervertebral space was reduced. The explanations for these findings are probably oedema and loosening of connective tissue, causing an increase in the bone volume of the spinal processes. Thus, the optimum puncture area on the skin for epidural space cannulation was smaller and the

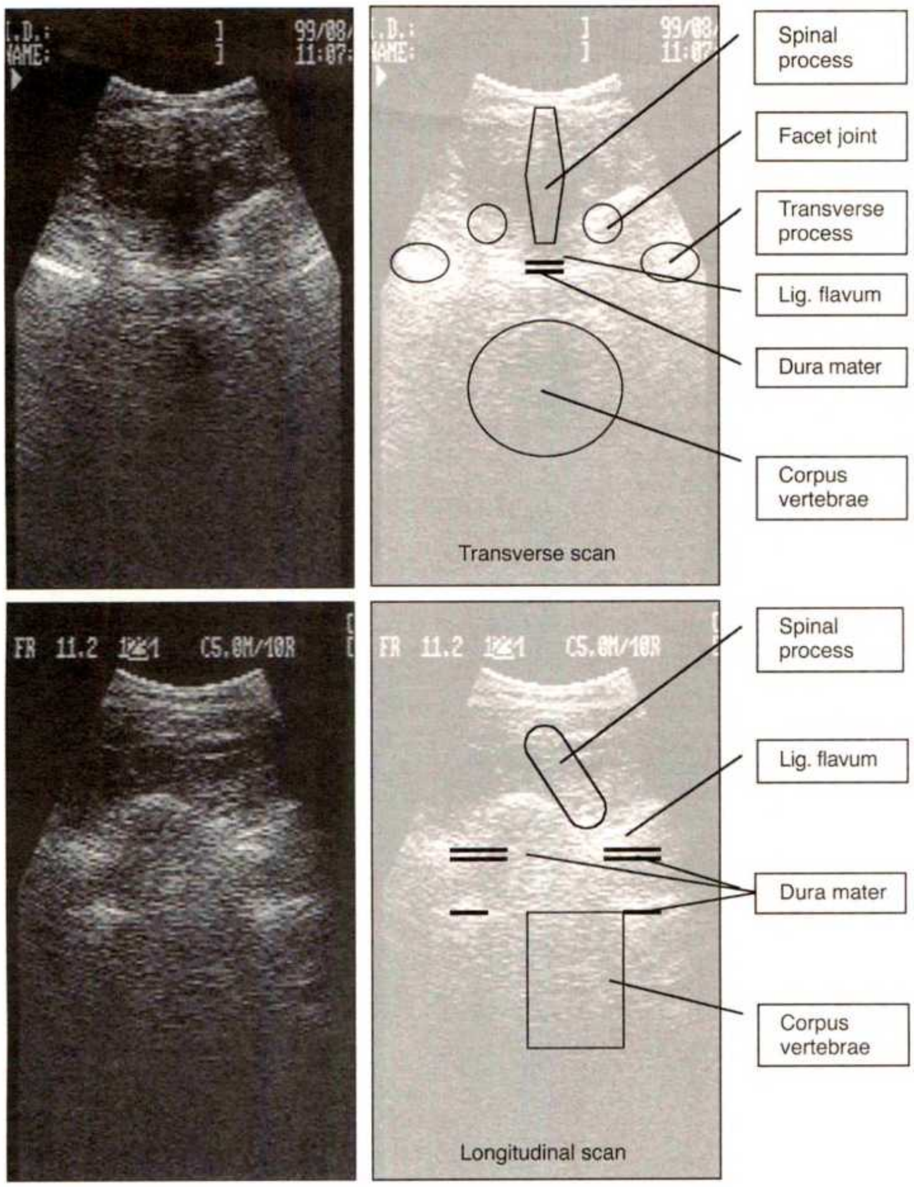

Fig 4 Perpendicular ultrasound scans of the same women 270 days after pregnancy with a graphic for the explanation of the localization.

soft-tissue channel between the spinal processes was narrower by the end of pregnancy. The distance from the skin to the epidural space was longer and the epidural space was narrower. Therefore, the 'safety zone' between transfixation of the ligamentum flavum and inadvertent dural puncture was smaller.

The quality the sonographic depiction of the key structures was reduced by pregnancy. Nevertheless, ultrasonography can be a valuable guide to epidural space puncture in parturients. The average quality of depiction is diminished in pregnancy 50–70% from the non-pregnant state, but was sufficient to identify the flaval ligament and the epidural space in all cases.

Segal and colleagues were one of the more recent groups attempting to relate the depth of the epidural space to the physical characteristics of the patients.[15] Like the preceding studies in this field,[16 17] their findings did not prove adequate for clinical use. Palpation is the only diagnostic method established for use during epidural puncture. Distance measurements other than by ultrasonography can only be obtained from a lateral radiograph of the lumbar spine or by computerized axial tomography, but radiography is an inappropriate diagnostic tool in pregnancy. Magnetic resonance imaging has expanded the diagnostic capabilities,[18 19] but is impractical in labour.

Ultrasonography is a promising technique for the assessment of spinal anatomy.[4 20] It is widely used during pregnancy, so parturients are familiar with it. The technique is free from adverse effects to mother and fetus. It is a mobile tool, which is readily available, even in the delivery room. There have been many advances in ultrasound imaging technology since earlier studies in this field were reported.[5–7] By the use of an advanced sonographic system we were able to identify the flaval ligament in nearly all cases, and the dura mater and, subsequently, the epidural space in many cases. Often, a three-dimensional impression could be acquired using two perpendicular scanning planes; thereby, enabling us to preview the anatomy of the lumbar spine. Thus, modern ultrasonography can be a valuable support before performing regional anaesthesia.

References

1 Herrera A, de las Mulas M. In memoriam Fidel Pages Mirave (1886–1923) on the 75th anniversary of the publication of 'Anesthesia metamerica'. *Rev Esp Anestesiol Reanim* 1996; **43**: 59–66

2 Reynolds A, Roberts P, Pollay M, Stratemeier P. Quantitative anatomy of the thoracolumbar epidural space. *Neurosurgery* 1985; **17**: 905–7

3 Blomberg RG. The dorsomedian connective tissue band in the lumbar epidural space of humans: An anatomical study using epiduroscopy in autopsy cases. *Anesth Analg* 1986; **65**: 747–52

4 Grau T, Leipold RW, Conradi R, Martin E, Motsch J. Ultraschall und Periduralanästhesie: Technische Möglichkeiten und Grenzen einer diagnostischen Untersuchung des Periduralraumes. *Anaesthesist* 2001; **50**: 54–101

5 Cork R, Kryc J, Vaughan R. Ultrasonic localization of the lumbar epidural space. *Anesthesiology* 1980; **52**: 513–6

6 Currie J. Measurement of the depth to the extradural space using ultrasound. *Br J Anaesth* 1984; **56**: 345–7

7 Wallace DH, Currie JM. Indirect sonographic guidance for epidural anaesthesia in obese pregnant patients. *Reg Anesth* 1992; **17**: 233–6

8 Bonazzi M, de Gracia LB. Individuazione ecoguidata dello spazio epidurale lombare. *Minerva Anestesiol* 1995; **61**: 201–5

9 Kelly RE, Verhage HG. Hormonal effects on the contractile apparatus of the myometrium. *Am J Anat* 1981; **161**: 375–82

10 Aspden RM. The theory of fibre-reinforced composite materials applied to changes in the mechanical properties of the cervix during pregnancy. *J Theor Biol* 1988; **130**: 213–21

11 Cittadini G, Martinoli C. Ultrasound and the bone: a difficult relationship. *Radiol Med (Torino)* 1995; **89**: 12–7

12 Cook TM. Combined spinal-epidural techniques. *Anaesthesia* 2000; **55**: 42–64

13 Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology* 1997: **87**: 479–86

14 Horlocker TT, McGregor DG, Matsushige DK, Schroeder DR, Besse JA. A retrospective review of 4767 consecutive spinal anesthetics: central nervous system complications. *Anesth Analg* 1997: **84**: 578–84

15 Segal S, Beach M, Eappen S. A multivariate model to predict the distance from the skin to the epidural space in an obstetric population. *Reg Anaesth* 1996; **21**: 451–455

16 Palmer SK, Abram SE, Maitra AM, von Colditz JH. Distance from the skin to the lumbar epidural space in an obstetric population. *Anesth Analg* 1983; **62**: 944–6

17 Harrison GR, Clowes NWB. The depth of the lumbar epidural space from the skin. *Anaesthesia* 1985; **40**: 685–7

18 Crighton IM, Barry BP, Hobbs GJ. A study of the anatomy of the caudal space using magnetic resonance imaging. *Br J Anaesth* 1997; **78**: 391–5

19 Westbrook JL, Renowden SA, Carrie LES: Study of the anatomy of the extradural region using magnetic resonance imaging. *Br J Anaesth* 1993; **71**: 495–8

20 Grau T, Leipold RW, Conradi R, Martin E, Motsch J. Ultrasound imaging facilitates localization of the epidural space during combined spinal–epidural anesthesia. *Reg Anaesth* 2001; **26**: 64–7

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Spinal anaesthesia for Caesarean section with bupivacaine 5 mg ml^{-1} in glucose 8 or 80 mg ml^{-1}

C. Connolly, G. A. McLeod and J. A. W. Wildsmith*

University Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

**Corresponding author*

The standard spinal preparation of bupivacaine contains a high concentration of glucose (80 mg ml^{-1}). However, the addition of only a small amount of glucose (8 mg ml^{-1}) to plain solutions of bupivacaine results in a solution which, although no more than marginally hyperbaric, produces a more predictable block when used for spinal anaesthesia in non-pregnant patients. However, bupivacaine 5 mg ml^{-1} in glucose 8 mg ml^{-1} has a density [1.00164 (SD 0.00008) at 37°C] which is relatively greater than that of the cerebrospinal fluid (CSF) of the pregnant patient at term (1.0003 at 37°C) because CSF density decreases during pregnancy. Therefore, a double-blind, randomized, controlled study was carried out to compare intrathecal bupivacaine (glucose 8 mg ml^{-1}) with bupivacaine (glucose 80 mg ml^{-1}) in 40 pregnant patients at term. Although there was no difference between groups in onset of sensory block, dose of ephedrine or patient satisfaction, patients receiving bupivacaine (5 mg ml^{-1}) with glucose (8 mg ml^{-1}) had persistently higher sensory blocks between 60 and 120 min after intrathecal injection, suggesting that the spread of spinal solutions in the pregnant patient at term is not dependent on density.

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Keywords: anaesthetics local, bupivacaine; anaesthetic techniques, regional, intrathecal; pregnancy

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Studies in non-pregnant subjects have shown that intrathecal bupivacaine 5 mg ml^{-1} in glucose 8 mg ml^{-1} produces blocks with a range (T10–T6) particularly suitable for most of the surgery for which spinal anaesthesia is appropriate.[1 2] Block of the lower limbs and lower abdomen is guaranteed, but spread to the level of the cardio-accelerator nerves is unlikely. In contrast, the standard preparation of bupivacaine contains glucose 80 mg ml^{-1} and produces unnecessarily extensive spread (T6–T2) for most operations.[3] However, this is the range of block generally considered necessary for Caesarean section. Therefore, a study was performed to compare these two solutions in pregnant patients at term.

Methods

Forty women (aged 18–40 yr) undergoing elective Caesarean section gave informed consent for this study, which was approved by the local research ethics committee (Tayside Committee on Medical Research Ethics). Patients at >37 weeks of gestation, >150 cm height and <110 kg weight (at time of delivery) were recruited; patients with pre-eclampsia, multiple pregnancies or placenta praevia were excluded from the study. After premedication with ranitidine 150 mg and 0.3 M sodium citrate 30 ml, and a preload of 500 ml crystalloid solution, patients were placed in the right lateral position with a pillow under the dependent shoulder. Under aseptic conditions, a 25 swg spinal Whitacre needle was introduced at the third lumbar interspace level with the needle port facing cephalad. The study solution (2.5 ml) was injected over 12.5 s and the end of injection was defined as time zero. Patients in group A received bupivacaine 5 mg ml^{-1} with glucose 8 mg ml^{-1} (prepared by mixing plain and hyperbaric solutions in the proportion of 9:1) and group B received bupivacaine 5 mg ml^{-1} with glucose 80 mg ml^{-1} (AstraZeneca, Kings Langley, UK). Allocation to groups was randomized using sealed envelopes, and the one investigator who assessed all the blocks did not know which solution had been used.

Immediately after lumbar puncture, patients were placed in the left, wedged position. Sensory block was determined using the blunt end of a 27 g dental needle at 2, 5, 10, 15, 20, 25 and 30 min, and every 15 min for 2 h thereafter. The extent of block was measured on both sides and an average

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Table 1 Patient characteristics, ephedrine requirements (mean and standard deviation) and numbers experiencing hypotension or requiring opioids in two groups of patients receiving spinal anaesthesia with bupivacaine 5 mg ml^{-1}. Group A received glucose 8 mg ml^{-1}; group B received glucose 80 mg ml^{-1}

	Group A	Group B
Age (yr)	29.8 (22–39)	32.0 (23–38)
Height (cm)	160.0 (6.6)	163.4 (7.0)
Weight (kg)	71.3 (9.5)	76.0 (11.3)
Ephedrine dose (mg)	23.7 (17.4)	15.9 (14.9)
Opioids given (*n*)	6	8
Hypotension (*n*)	3	3
Patient satisfaction (excellent/very good)	16/3	16/3

Table 2 Sensory block characteristics (mean and standard deviation) in two groups of patients receiving spinal anaesthesia with bupivacaine 5 mg ml^{-1}. Group A received glucose 8 mg ml^{-1}; group B received glucose 80 mg ml^{-1}

	Group A	Group B
Onset time at T4 (min)	13.3 (9.8)	14.7 (6.5)
Time to maximum block height (min)	20.0 (8.4)	20.0 (6.9)
Two-segment regression (min)	69.2 (31.3)	69.0 (20.3)
Regression to T10 (mg)	127.1 (20.8)	105.0 (25.3)
Time to first post-operative request for morphine (min)	101.5 (35.1)	87.8 (31.0)

taken if there was a difference. Blood pressure was measured pre-operatively, every 2 min for 10 min and then every 5 min for 2 h after lumbar puncture. Hypotension (defined as a systolic blood pressure more than 30% below the pre-operative figure or symptoms related to poor perfusion, such as nausea or dizziness) was treated with ephedrine 6 mg i.v. The spinal anaesthetic was supplemented with i.v. increments of either alfentanil or morphine as required.

Post-operatively, all patients received diclofenac 100 mg per rectum. The time to first morphine requirement was noted and the first dose was given i.v. by an investigator. The density of both solutions was measured to five decimal places at 37°C with a digital density meter using the oscillation frequency method (DE50; Mettler Toledo, Leicester, UK).

Statistical analysis of results was performed with Statview (Palo Alto, CA, USA). Patient characteristics, sensory block times and blood pressures were compared using the *t*-test with Bonferroni correction as appropriate. Sensory block height was compared using the Mann–Whitney *U*-test.

Results

There were no differences between the groups with respect to patient characteristics (Table 1). Speed of onset of sensory block, time to maximum sensory block (Table 2) and median maximum block height (Fig. 1) were the same in both groups. In five patients in group A and two in group B, the block extended to the cervical dermatomes. Intra-operative opioid supplementation was required by six patients in group A and eight in group B. Patient satisfaction scores were equivalent: 16 patients in each group regarded their anaesthesia as 'excellent'. Although there was no statistically significant difference in two-segment regression, regression to T10 or time to first request for morphine, median block was higher at 60, 90, 105 and 120 min (Fig. 1) in the group which received glucose 8 mg ml^{-1}. No statistically significant difference existed between the groups with regard to cardiovascular changes or ephedrine requirement, although there was a tendency towards a lower systolic blood pressure after delivery in those receiving glucose 8 mg ml^{-1} (Fig. 2). The density of bupivacaine 5 mg ml^{-1} in glucose 8 mg ml^{-1} (group A) was 1.00164 (SD 0.00008) and bupivacaine 5 mg ml^{-1} in glucose 80 mg ml^{-1} (group B) 1.02081 (0.00017).

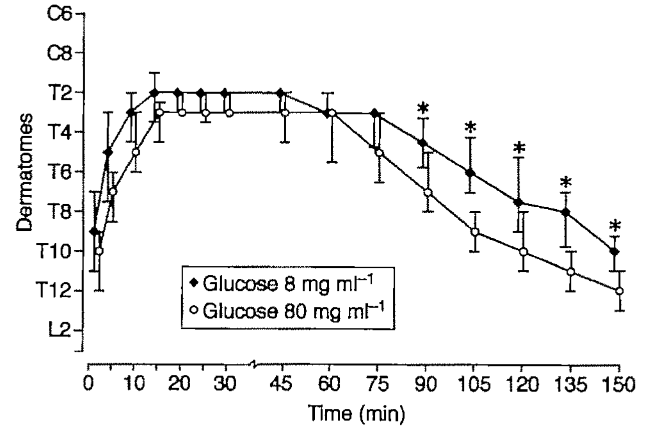

Fig 1 Changes in median (with interquartile range) maximum block height over time in two groups of patients receiving spinal anaesthesia with bupivacaine 5 mg ml^{-1}. *$P<0.05$.

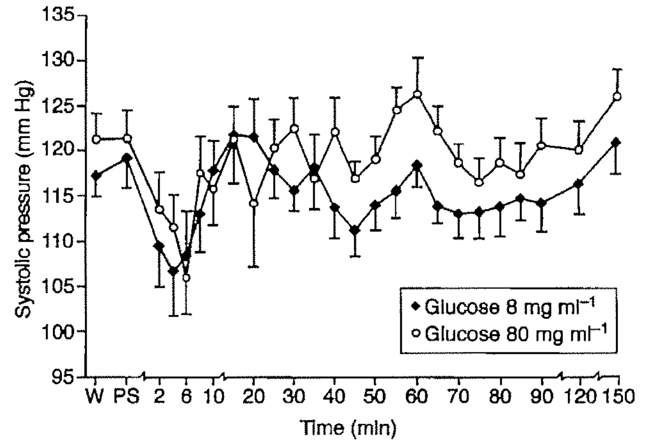

Fig 2 Changes in mean (with standard deviation) systolic blood pressure over time in two groups of patients receiving spinal anaesthesia with bupivacaine 5 mg ml^{-1}. W, ward; PS, pre-spinal.

Discussion

This study has shown that a tenfold difference in glucose concentration has little effect on the spread of bupivacaine after intrathecal injection in pregnant patients at term. There were virtually no differences between the two groups in the profile of the blocks produced or in the quality of surgical anaesthesia. This is in marked contrast to the situation in the non-pregnant subject, where a high concentration of glucose is needed to ensure spread to the upper thoracic segments in supine horizontal subjects.[1 2] In fact, even plain solutions of bupivacaine will produce spread to that level when used for Caesarean section.[4] It is generally recognized that baricity is the most important factor determining the spread of local anaesthetic in the non-pregnant patient,[5 6] but this is clearly not the case in the pregnant patient at term. It is interesting to consider why this might be so.

Baricity is the ratio of the density of a local anaesthetic solution compared with that of cerebrospinal fluid (CSF).[7] If the patient is turned supine after injection in the lumbar region, a hyperbaric solution will spread under the influence of gravity down the slopes created by the lumbar spinal curvature. Bupivacaine 5 mg ml^{-1} in glucose 8 mg ml^{-1} has a density (1.00164 at 37°C) that is only marginally greater than that of normal adult CSF [1.0007 (SD 0.0003) at 37°C], so that it will spread more slowly than the standard preparation with glucose 80 mg ml^{-1} (density 1.02081 at 37°C). The actual concentration of the dilute preparation is crucial: an increase to only 10 mg ml^{-1} produces blocks that are almost indistinguishable from those produced by much higher concentrations.[8] However, CSF density decreases with CSF protein concentration during pregnancy, reaching a minimum [1.0003 (0.0004) at 37°C] at term.[10 11] Thus, the difference in density between CSF and the solution containing glucose 8 mg ml^{-1} will be greater than in the non-pregnant patient and thus result in more extensive spread.

This analysis would account for the lack of difference between the two groups reported here, but not for the extensive spread of plain bupivacaine (0.9993 at 37°C) in pregnant patients. This solution is hypobaric relative to CSF even at term. The generally accepted reason is that the exaggerated spread is a consequence of occlusion of the inferior vena cava being only partially relieved in the left, wedged supine position. Distention of the veins of the vertebral plexus causes compression of the dura, reduces CSF volume and encourages greater bulk spread of the injected solution. This is clearly the major factor at the end of pregnancy. However, it is interesting to note that this study produced some evidence that physical characteristics of the local anaesthetic solutions were having some influence, most notably that a prolonged offset of block occurred in those receiving the less dense solution (Fig. 1). This suggests that a greater proportion of the injected solution spread more cephalad, but that this effect cannot be attributed to density. As glucose concentration increases, the solution becomes not only denser but also more viscous. A less viscous solution would flow more easily through a compressed subarachnoid space, allowing a greater proportion of the injected dose to reach the thoracic nerves and cause a longer duration of action.

In conclusion, this study has shown that density has little effect on the intrathecal spread of local anaesthetics at the end of pregnancy, and therefore that the glucose concentration of a spinal anaesthetic solution is of little consequence in this group of patients. The major reason for this is probably a secondary effect of partial inferior vena cava obstruction, although the viscosity of the injectate may have some influence. One fortunate consequence of this independence of intrathecal drug spread from density is that a change, as may be produced by mixing the local anaesthetic with an opioid solution, would not have the same possible consequences as in the non-pregnant population.

Acknowledgements

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References

1 Bannister J, McClure JH, Wildsmith JAW. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine. *Br J Anaesth* 1990; **64**: 232–4

2 Sanderson P, Read J, Littlewood DG, McKeown D, Wildsmith JAW. Interaction between baricity (glucose concentration) and other factors influencing intrathecal drug spread *Br J Anaesth* 1994; **73**: 744–6

3 Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *Br J Anaesth* 1981; **53**: 279–82

4 Russell IF, Holmqvist ELO. Subarachnoid analgesia for caesarean section. A double blind comparison of plain and hyperbaric 0.5% bupivacaine. *Br J Anaesth* 1987; **59**: 347–53

5 Greene NM. Distribution of local anaesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; **64**: 715–30

6 McClure JH, Wildsmith JAW. Aspects of spinal anaesthesia. In: Kaufman L, ed. *Anaesthesia Review 5*. Edinburgh: Churchill Livingstone, 1987; 269–85

7 Connolly C, Wildsmith JAW. Intrathecal drug spread. *Can J Anaesth* 1998; **45**: 289–92

8 Lee A, Ray D, Littlewood DG, Wildsmith JAW. Effect of dextrose concentration on the intrathecal spread of amethocaine. *Br J Anaesth* 1988; **61**: 135–8

9 Lui ACP, Polis TZ, Cicutti, Nicholas J. Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. *Can J Anaesth* 1998; **45**: 297–303

10 Richardson MG, Wissler RN. Density of lumbar cerebrospinal fluid in pregnant and nonpregnant humans. *Anesthesiology* 1996; **85**: 326–30

11 Richardson MG, Wissler RN. Densities of dextrose-free intrathecal local anesthetics, opioids, and combinations measured at 37C. *Anesth Analg* 1997; **84**: 95–9

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Does prior administration of enoxaparin influence the effects of levobupivacaine on blood clotting? Assessment using the Thrombelastograph®

S. A. Leonard[1], A. Lydon[2], M. Walsh[3], C. Fleming[4], J. Boylan[2] and G. D. Shorten[1]*

[1]Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital and University College, Cork, Ireland. [2]Department of Anaesthesia, St Vincent's Hospital, Dublin, Ireland. [3]Department of Anaesthesia, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland. [4]Department of Biochemistry, St Vincent's Hospital, Dublin, Ireland

**Corresponding author*

The low molecular weight heparin, enoxaparin (by inhibition of factors Xa and IIa) and amide local anaesthetics (by altering platelet function) exert anti-clotting effects. Although these agents are often used in combination during the perioperative period, their potential interactive effect on clotting has not been defined. Blood from 10 ASA I–II patients who received enoxaparin 0.5 mg kg^{-1} s.c. was studied using a Thrombelastograph (TEG®) either alone or in combination with levobupivacaine (2.5 mg ml^{-1} or 2.5 μg ml^{-1}) or saline (50% dilution). In blood from patients who had received enoxaparin 0.5 mg kg^{-1} s.c. 12 h previously, levobupivacaine 2.5 mg ml^{-1} (but not 2.5 μg ml^{-1}) produced significant changes in TEG clotting parameters (mean (SD) 15.7 (4.8) mm, 29.6 (25.6) mm, 34.4 (14.6) mm, 34.3 (12.2)° compared with control values of 6.1 (1.3) mm, 2.5 (0.5) mm, 63.5 (6.4) mm and 74.1 (2.9)° for *r*, *K*, MA, and α angle respectively).

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Venous thromboembolism is a major complication of lower limb orthopaedic surgery and associated pulmonary embolism is an important cause of perioperative death.[1] Prophylactic subcutaneous heparin decreases the incidence of deep venous thrombosis (DVT) from 24 to 10% after hip surgery[1] and from 60 to 40% after knee surgery.[2] Low molecular weight heparins (LMWH) such as enoxaparin sodium (Lovenox, Clexane, Aventis™, Strasburg, France) have been shown to be as effective and safe as low dose unfractionated heparin (UFH).[3–5] Using the Thrombelastograph (TEG®), enoxaparin (at anti-Xa activity concentrations of 0.1–0.3 unit ml^{-1}) has been shown *ex vivo* to produce a dose dependent increase in reaction time (*r*), (a measure of the rate of fibrin formation) and coagulation time (*K*), and a decrease in α angle (the rate of clot formation).[6]

Neuraxial block provides excellent operating conditions for lower limb surgery, good postoperative analgesia and decreases blood loss and the incidence of DVT.[2–4 6–8] The safety of spinal or epidural techniques in patients who have received prophylactic enoxaparin is controversial.[9 10] The prescribing information for enoxaparin contains a warning of the risk of spinal haematoma when the drug is used in combination with neuraxial block. More than 60 cases of epidural haematomata associated with the administration of enoxaparin in conjunction with neuraxial block have been reported.[11] The risk is probably greater in elderly females, when epidural catheters are used and when a dose of 30 mg bd rather than 40 mg once daily is administered.[12]

Amide local anaesthetics such as levobupivacaine are potent inhibitors of platelet aggregation and release.[13 14] Levobupivacaine has recently been approved for clinical use and is likely to be commonly used for epidural anaesthesia. The anti-platelet effects of levobupivacaine are reflected on thromboelastography as a dose dependent decrease in maximum amplitude (a measure of clot formation).[15]

LMWHs, in combination with non-steroidal anti-inflammatory drugs, prolong bleeding time.[16 17] It is now recommended that this combination should not be given to patients undergoing surgery under central nerve block.[11 12] Non-steroidal anti-inflammatory drugs, like local anaesthetics, exert their anti-coagulant action, in

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part, by inhibition of platelet aggregation. To date, the potential interactive effect of enoxaparin and amide local anaesthetic agents on blood clotting has not been examined.

The aim of this study was to assess, using thromboelastography, the effect of levobupivacaine on clotting of blood from patients who have received enoxaparin 12 h previously.

Methods

With institutional ethical approval, and having obtained written informed consent, 10 ASA I–II patients (aged 28–60 yr) undergoing elective lower limb orthopaedic surgery were studied. Only patients who required anticoagulant prophylaxis with enoxaparin for clinical reasons were recruited. Patients with a history of allergy to heparin or local anaesthetics, a disorder of platelet function, coagulation or fibrinolysis or those who were taking any drug known to affect these systems were excluded.

On the night before surgery, a venous cannula was sited in the patient's non-dominant forearm. A two-syringe technique was used to withdraw 11 ml of blood. The initial 2 ml was discarded to decrease tissue thromboplastin contamination. The remainder was divided between two polypropylene tubes, each containing 0.5 ml of 3.2% sodium citrate. These were analysed for:

1.Factor Xa activity. Blood (4.5 ml) from the first citrated tube was centrifuged at 240 *g* at 4°C for 10 min. The plasma samples were stored at –70°C and the assay carried out within 1 month of collection.

2.TEG parameters. After 30 min 1000 μl of blood from the other citrated tube was transferred to a celite 1% vial of which 340 μl was transferred to a TEG® cup and analysed as below (sample S_1 in Figs 1–4).

Enoxaparin 0.5 mg kg^{-1} (Clexane®, Aventis™, Ireland) was administered s.c. after the control venous samples had been taken (this avoided the relative overdose that may occur in smaller patients).[18]

On the morning of surgery, 12 h after the administration of the enoxaparin, a further 11 ml of blood was taken using a two-syringe technique as described and the blood analysed for factor Xa activity. Blood was collected and stored as for the first sample. Coagulation analysis was carried out on whole blood, blood/saline as a control for dilution effects, and two blood/levobupivacaine solutions. Citrated whole blood, 1000 μl, was transferred to each of four celite™ 1% (Haemoscope Corp., Skokie, IL, USA) bottles to produce four solutions as follows:

S_2: Whole blood 340 μl was recalcified with 20 μl of RECAL™ (to assess the effect of enoxaparin alone).

S_3: Whole blood 160 μl and NaCl 0.9% 180 μl with 20 μl RECAL™ (to assess the effects of dilution).

S_4: Whole blood 160 μl and levobupivacaine 5 mg ml^{-1} 180 μl with RECAL™ 20 μl (to produce an end concentration of 2.5 mg ml^{-1}) (to mimic the concentration if a mixture occurred of levobupivacaine 0.5% and whole blood in equal quantities in the epidural space).

S_5: Whole blood 331.7 μl and levobupivacaine 10 μg ml^{-1} 8.3 μl with RECAL™ 20 μl (to produce an end

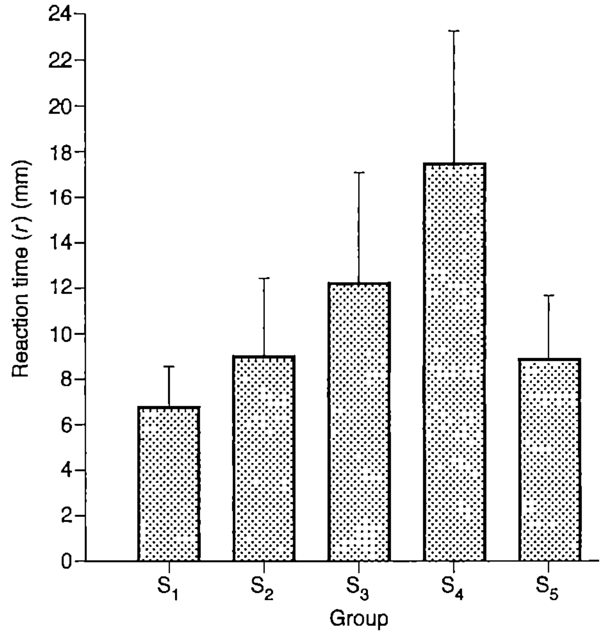

Fig 1 Mean (SD) reaction time (*r*) in whole blood pre-enoxaparin (S_1), whole blood from patients who had received enoxaparin 0.5 mg kg^{-1} s.c. 12 h previously (blood$_e$)(S_2), blood$_e$ diluted 50% with saline (S_3), blood$_e$/levobupivacaine 2.5 mg ml^{-1} (S_4), blood$_e$/levobupivacaine 2.5 μg ml^{-1} (S_5). See text for significances.

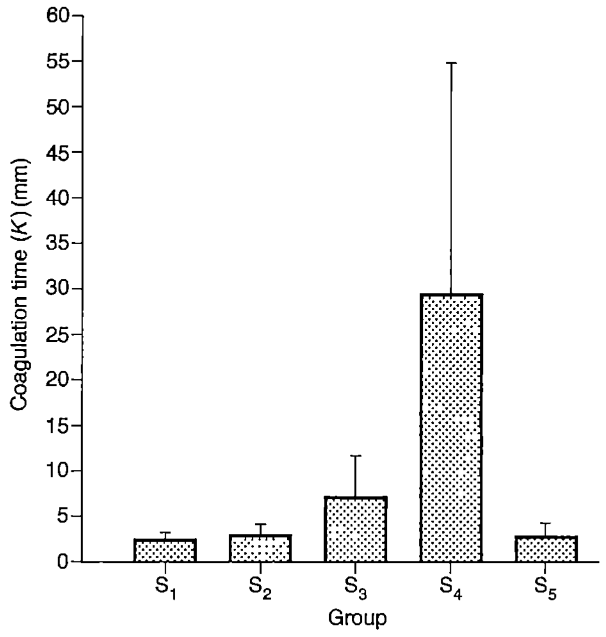

Fig 2 Mean (SD) coagulation time (*K*) in whole blood pre-enoxaparin (S_1), whole blood from patients who had received enoxaparin 0.5 mg kg^{-1} s.c. 12 h previously (blood$_e$)(S_2), blood$_e$ diluted 50% with saline (S_3), blood$_e$/levobupivacaine 2.5 mg ml^{-1} (S_4), blood$_e$/levobupivacaine 2.5 μg ml^{-1} (S_5). See text for significances.

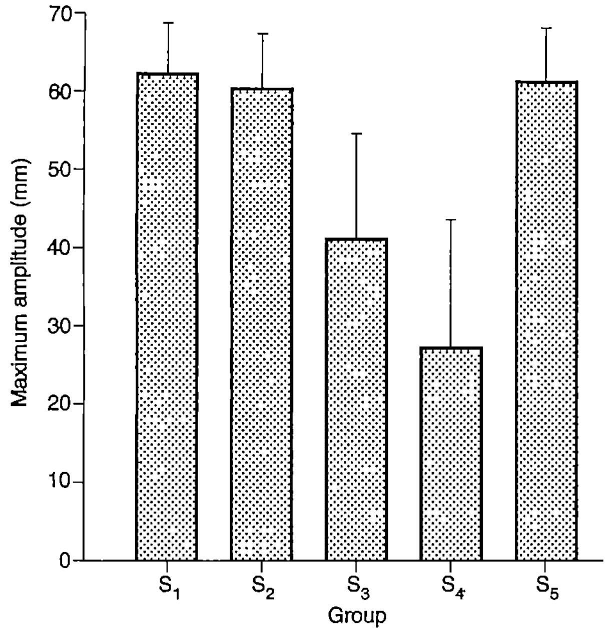

Fig 3 Mean (SD) maximum amplitude (MA) in whole blood pre-enoxaparin (S_1), whole blood from patients who had received enoxaparin 0.5 mg kg^{-1} s.c. 12 h previously (blood_e)(S_2), blood_e diluted 50% with saline (S_3), blood_e/levobupivacaine 2.5 mg ml^{-1} (S_4), blood_e/levobupivacaine 2.5 μg ml^{-1} (S_5). See text for significances.

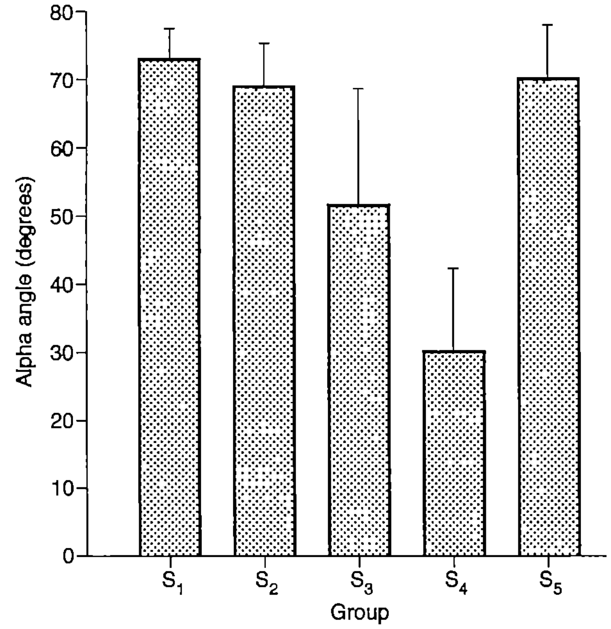

Fig 4 Mean (SD) alpha angle (α angle) in whole blood pre-enoxaparin (S_1), whole blood from patients who had received enoxaparin 0.5 mg kg^{-1} s.c. 12 h previously (blood_e)(S_2), blood_e diluted 50% with saline (S_3), blood_e/levobupivacaine 2.5 mg ml^{-1} (S_4), blood_e/levobupivacaine 2.5 μg ml^{-1} (S_5). See text for significances.

concentration of 2.5 μg ml^{-1}) (to mimic the concentration in the systemic circulation after bolus epidural administration of local anaesthetic).

Levobupivacaine solutions were prepared using levobupivacaine hydrochloride 5 mg ml^{-1} (Abbott Laboratories Ltd, Ireland) in 0.9% saline.

Biochemical analysis

The samples were analysed for plasma anti-factor Xa activity in a single batch. An amidolytic assay using a commercially available kit (Chromostrate™, Organon Teknika Corp., Boxtel, The Netherlands) and a spectrophotometer set at 405 nm were used. The assay has a minimum detection limit of 0.01 anti-factor Xa unit ml^{-1}.

Thromboelastography

A pre-warmed computerized TEG® machine (Haemoscope 2000D®, Haemoscope Corp., IL, USA) was used with standard calibrations for strain, alignment, balance and clearance. Each TEG® cup at 37°C was filled with a total of 340 μl of blood, blood/levobupivacaine solution or blood/saline and recalcified with RECAL™ 20 μl. Three drops of mineral oil was applied to the upper surface. Celite-activated thromboelastography profiles were recorded until *Ly 30* was achieved. The morphology and data for four TEG® parameters were collected and stored.

Based on an $\alpha=0.05$ and $\beta=0.2$ and previous work (66% decrease in MA by racemic bupivacaine 2.5 mg ml^{-1}[19]) power analysis indicated a minimum sample size of 10 was necessary to detect a 50% effect on MA with an SD for residuals of 30%.

Data were analysed using one-way ANOVA and a Student Newman–Keuls test using the Sigma Stat™ software (Jandel Scientific Corporation Version 1). $P<0.05$ was considered significant. All data are expressed as mean (SD).

Results

Ten ASA I patients (six female, four male, age 40.1 (12.8) yr, weight 77.6 (17.4) kg) undergoing elective orthopaedic surgery were studied. All the values for whole blood (S_1) were within normal limits (*r* values, although less than those quoted for celite-activated whole blood[20] were similar to those achieved after recalcification[21]) (Figs 1–4). Anti-Xa activity was not detectable in the pre-enoxaparin sample (S_1) and was 0.17 (0.08) unit ml^{-1} 12 h later.

The blood of patients treated with enoxaparin 12 h previously (S_2) was similar in all parameters to the pre-enoxaparin controls (S_1) (Figs 1–4). Maximum amplitude and α angle were less in the saline controls (S_3, enoxaparin-treated blood/saline) than in whole blood controls (S_1) and enoxaparin-treated whole blood (S_2) (MA=41.3 (13.5) mm, for S_3 *vs* 62.5 (6.0) mm for S_1 and 60.6 (7.2) for S_2, α angle=51.5 (17.3)° for S_3 *vs* 73.2 (4.6)° for S_1 and 69.4 (6.3)° for S_2) (Figs 3 and 4). In blood of patients who had received enoxaparin 12 h previously the following results were found: (1) dilution (50%) with saline resulted in an increase in MA (41.3 (13.5) mm) and α angle (51.5 (17.3)°) ($P<0.05$), (2) levobupivacaine 2.5 mg ml^{-1} (S_4) (but not 2.5 μg ml^{-1}) resulted in an increase in *r* (17.5 (17.5) mm) and *K* (29.6 (25.6) mm) and a decrease in MA (27.2 (16.8) mm) and α angle (29.8 (12.5)°) (all $P<0.05$) compared with the pre-enoxaparin controls (6.8 (1.8) mm, 2.6 (1.5) mm, 62.5 (6.0) mm, 73.2 (4.6)° for *r*, *K*, MA, and α angle, respectively), (3) the alterations in *r*, *K*, MA, and α angle produced by the levobupivacaine 2.5 mg ml^{-1} (S_4) were also significantly greater than those produced by 50% dilution with saline (S_3) and (4) addition of levobupivacaine 2.5 mg ml^{-1} (S_4) produced a significant alteration in *r*, *K*, MA, and α angle compared with the whole blood similarly treated with enoxaparin (S_2) (*r*, *K*, MA, and α angle for S_2=9.0 (3.4) mm, 3.1 (1.2) mm, 60.6 (7.2) mm and 69.4 (6.3)°, respectively) (Figs 1–4).

Discussion

The most important finding of this study is that levobupivacaine produces a dose dependent decrease in clotting of whole blood from patients previously treated with enoxaparin. In this preparation (levobupivacaine 2.5 mg ml^{-1} in whole blood from patients who had received enoxaparin 12 h previously), the indices of clot formation (*r*, *K*, MA, α angle), measured with thromboelastography demonstrated impaired clotting. The results were also significantly different from the saline control (50% dilution of whole blood with saline) indicating that the impairment cannot be ascribed to dilution alone.

Enoxaparin is a LMWH, which exerts an anti-coagulant effect by inhibition of factor Xa and IIa (thrombin) in the ratio 2.7:1.[22] This is reflected on TEG® by a dose dependent increase in reaction time (*r*) and a decrease in α angle.[6] Maximum anti-Xa activity occurs 4 h after subcutaneous injection and at 12 h is still up to 50% of this.[22] It produces effective prophylaxis for thromboembolism after lower limb joint replacement.[2–5] Since 1993, there have been more than 60 reports of spinal haematomata occurring when neuraxial block is used concurrently with enoxaparin prophylaxis.[11] Analysis of these cases indicates that insertion of an epidural catheter, extreme age, a dose of 30 mg bd and the concomitant use of anti-platelet medication increase the risk.[10 12]

We did not demonstrate a clotting defect on the TEG® in blood from patients treated with a single dose of enoxaparin 12 h previously. In this study, anti-Xa activity was 0.17 (0.08) unit ml^{-1} with a range of 0.06–0.31 unit ml^{-1}. Previous workers have also demonstrated a wide variability in plasma anti-Xa activity achieved after a single dose of enoxaparin.[23 24] Thrombosis is inhibited at anti-factor Xa concentrations of 0.2–0.3 unit ml^{-1} in an animal model.[25] Anti-factor Xa activity in four out of 10 patients was within this range at 12 h. Our results demonstrate that this effect in isolation is not sufficient to alter clotting to an extent that is detectable by TEG®. The significance of these contrasting results is unclear. Current guidelines recommend that neuraxial block can be safely carried out 12 h or more after administration of enoxaparin 40 mg s.c. but the large controlled studies that would be required to detect any difference in incidence of spinal haematoma with concurrent use of LMWH have not been carried out.[18]

The effects of a number of amide local anaesthetics on coagulation and fibrinolysis have previously been assessed using thromboelastography.[15 16 27–30] Racemic bupivacaine, levobupivacaine, ropivacaine and lignocaine *in vitro* decrease MA in a concentration dependent manner.[19 26–29] Lignocaine and ropivacaine increase *K* at high concentrations.[28 29] A decrease in α angle is produced by lignocaine, racemic bupivacaine and ropivacaine.[19 26 28 29] Levobupivacaine 2.5 mg ml^{-1} alone (in blood of volunteers) produced a decrease in MA only (mean reduction in MA of 13.5% compared with 35.3% with the levobupivacaine 2.5 mg ml^{-1} enoxaparin combination).[15] Enoxaparin alone did not significantly alter clotting. However, the addition of levobupivacaine 2.5 mg ml^{-1} to the blood of patients previously treated with enoxaparin produced a prolongation of *r* and *K*, and a decrease in α angle in addition to the augmented effect on MA. This result suggests that the presence of enoxaparin enhances the anti-clotting effects of levobupivacaine.

Platelet aggregation and coagulation are interdependent processes leading to thrombus formation. Cytoplasmic ionized calcium is the key 'second messenger' in platelet activation. Calcium dependent activities include aggregation, clot retraction and secretion of the contents of storage granules.[31] It is also essential for the activation of the 'lipid scramblase'.[32] This induces surface expression of platelet membrane phospholipid, which promotes binding and catalytic activity of IXa and Xa leading to thrombin formation.[32] In the resting platelet, ionized calcium is concentrated in the plasma membrane, the dense tubular system and the storage granules. Thrombin induces platelet activation by stimulating release of calcium from intracellular stores and an increase in cytosolic free calcium.[33] Local anaesthetics inhibit platelet aggregation and secretion by block of calcium mobilization from intra-platelet storage pools and calcium influx across the platelet membrane.[13 14 34 35] Heparins also decrease calcium mobilization within the platelets inhibiting thrombin-induced platelet activation.[36] Both LMWHs and local anaesthetics may diminish the increase in platelet cytosolic ionized calcium normally associated with platelet activation. This is one potential explanation for the effect on MA seen in this study with the addition of levobupivacaine 2.5 mg ml^{-1} to enoxaparin-treated blood. The effect of the levobupivacaine/enoxaparin combination on *r* and *K* parameters which are dependent on the coagulation cascade, may be because of a decrease in cytosolic ionized calcium and inhibition of lipid scramblase reducing factor Xa binding and activity.

No effect on TEG® parameters was demonstrated with the levobupivacaine 2.5 μg ml^{-1} solution when compared with controls. This indicates that the effect is concentration dependent and that levobupivacaine at concentrations produced systemically after an epidural bolus are unlikely to increase the effect of enoxaparin on clotting.

A number of limitations apply to this study. We did not correct for the effect of 50% dilution on calcium or pH as previous studies have shown this to be minimal.[37] Our samples were citrated and assessed after recalcification. This process can alter coagulation parameters as assessed with the Thrombelastograph®.[20] Blood recalcified after 30 min demonstrates a decrease in *r*, *K* and MA and an increase in the α angle. The magnitude of these effects is small (~5%) relative to those demonstrated in our levobupivacaine (2.5 mg ml^{-1})/enoxaparin combination (~55–250%). The mixing of levobupivacaine solutions with blood occurred *ex vivo* and so the effect of endothelial surface on clotting function was not assessed. The saline control had a significantly decreased MA and α angle when compared with whole blood control. This is consistent with the work of Tobias and colleagues who demonstrated that 50% dilution causes a decrease in α angle and MA.[38] This is the degree of dilution which we produced in the saline control and in the levobupivacaine 2.5 mg ml^{-1} preparation. The effect on clotting produced by this solution can, therefore, be attributed, in part, to dilution. All indices of clot formation (*r*, *K*, MA and α angle), however, were significantly impaired even when compared with the similarly diluted control. This impairment, therefore, represents an additional effect of the levobupivacaine/enoxaparin combination.

This is the first study to assess whether an amide local anaesthetic can enhance the anti-clotting effects of enoxaparin. We have demonstrated that such an effect does occur at a concentration of levobupivacaine of 2.5 mg ml^{-1}. This observation may have important clinical implications. Spinal haematoma is a rare but potentially devastating consequence of neuraxial block in patients receiving LMWH. One of the factors, which appear to increase the risk, is the use of epidural catheters.[18] This effect may at least in part be explained by the influence of the local anaesthetic solution infused or injected into the epidural space.

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References

1 Dalldorf PG, Perkins FM, Totterman S, Pellegrini VD. Deep venous thrombosis following total hip arthroplasty. Effects of prolonged postoperative epidural. *J Arthroplasty* 1994; **9**: 611–6

2 Planes A, Vochelle N, Ribeyrol JL, Fagola M, Neuhart E. Enoxaparin in prevention of venous thrombosis following total knee replacement under spinal anaesthesia. SICOT 90 XVIII World Congress, Montreal, 9–14 September, 1994

3 Colwell CW Jr, Spiro TE. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip arthroplasty. *Clin Orthop* 1995; **319**: 215–22

4 Turpie AGG, Levine MN, Hirsh J, *et al.* A randomized controlled trial of a low molecular weight heparin (enoxaparin) to prevent deep venous thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986; **315**: 925–9

5 Martineau P, Tawil N. Low molecular-weight heparins in the treatment of deep-vein thrombosis. *Ann Pharmacother* 1998; **32**: 588–98

6 Gottlieb A, Mraovic B, Sprung J, Potter P, Kottke-Marchant K. The usefulness of thromboelastography in determining the coagulation effects of low-molecular weight heparin. *Anesth Analg* 1999; **88**: S1–424

7 Henny CP, Odoom JA, ten Cate H, Oosterhof RJF, Dabhoiwala NF, Sih IL. Effects of extradural bupivacaine on the haemostatic system. *Br J Anaesth* 1986; **58**: 301–5

8 Sharrock NE, Salvati EA. Hypotensive epidural anaesthesia for total hip arthroplasty: a review. *Acta Orthop Scand* 1996; **67**: 91–107

9 Bergqvist D, Lindblad B, Matzsch T. Low molecular-weight heparin for thromboprophylaxis and epidural/spinal—is there a risk? *Acta Anaesthesiol Scand* 1992; **36**: 605–9

10 Checketts MR, Wildsmith JAW. Central nerve block and thromboprophylaxis – is there a problem? *Br J Anaesth* 1999; **82**: 164–7

11 Lovenox® (enoxaparin sodium), Aventis® US. Manufacturers prescribing information 12/98

12 Horlocker TT, Wedel DJ. Spinal and epidural block and perioperative low molecular weight heparin: smooth sailing on the Titanic. *Anesth Analg* 1998; **86**: 1153–6

13 Feinstein MG, Fiekers J, Fraser C. An analysis of the mechanism of local anaesthetic inhibition of platelet aggregation and secretion. *J Pharmacol Ther* 1976; **197**: 215–28

14 Borg T, Modig J. Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. *Acta Anaesthesiol Scand* 1985; **29**: 739–42

15 Leonard SA, Walsh M, Lydon A, O'Hare B, Shorten GD. Evaluation of the effects of levobupivacaine on clotting and fibrinolysis using thromboelastography. *Eur J Anaesthesiol* 2000; **17**: 373–8

16 Delaporte-Cerceau S, Samama CM, Riou B, Bonnin P, Guillosson JJ, Coriat P. Ketorolac and enoxaparin affect arterial thrombosis and bleeding in the rabbit. *Anesthesiology* 1998; **88**: 1310–7

17 Greer IA, Gibson JL, Young A, Johnstone J, Walker ID. Effect of ketorolac and low-molecular-weight heparin individually and in combination on haemostasis. *Blood Coagul Fibrinolysis* 1999; **19**: 367–73

18 Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; **85**: 874–85

19 Tobias MD, Pilla MA, Rogers C, Jobes DR. Lidocaine inhibits blood coagulation: implications for epidural blood patch. *Anesth Analg* 1996; **82**: 766–9

20 Yamakage M, Tsujiguchi N, Kohro S, Tsuchida H, Namiki A. The usefulness of celite-activated thromboelastography for evaluation of fibrinolysis. *Can J Anaesth* 1998; **45**: 993–6

21 Camenzind V, Burkhardt S, Zollinger A, Popovic D, Jamnicki M, Pasch T, Spahn D. Citrate storage alters blood coagulation

parameters as assessed by thromboelastography. *Anesthesiology* 1998; **89**: A915

22 Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992; **79**: 1–17

23 Eriksson BI, Soderberg K, Widlund L, Wandell B, Tengborn L, Risberg B. A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers. *Thromb Hemost* 1995; **73**: 398–401

24 Azizi M, Veyssier-Belot C, Alhenc-Gelas M, *et al.* Comparison of biological activities of two low molecular weight heparins in 10 healthy volunteers. *Br J Clin Pharmacol* 1995; **40**: 577–84

25 Bone B, Buchanan MR, Cade JF, *et al.* Effects of heparin, its low molecular weight fractions and other glycosaminoglycans on thrombus growth in vivo. *Thromb Res* 1985; **40**: 81–9

26 Tobias MD, Henry C, Augostides YG. Lidocaine and bupivacaine exert differential effects on whole blood coagulation. *J Clin Anesth* 1999; **11**: 52–5

27 Kohrs R, Hoenemann CW, Feirer N, Durieux ME. Bupivacaine inhibits whole blood coagulation *in vitro*. *Reg Anesth Pain Med* 1999; **24**: 326–30

28 Pan PH, Moore C, Fragneto RY, Ross VH, Justis G. Different epidural local anesthetics may affect the success rate of prophylactic epidural blood patch. *Anesth Analg* 1999; **88**: S262

29 Ti LK, Lee TL. Inhibition of coagulation by local anesthetics: a comparison of lidocaine, bupivacaine and ropivacaine. *Anesth Analg* 1999; **88**: S282

30 Porter JM, McGinley J, O'Hare B, Shorten GD. The effects of ropivacaine hydrochloride on coagulation and fibrinolysis. *Anaesthesia* 1999; **54**: 902–6

31 Jacek H, Brass LF, Salzman EW. Signal transduction and intracellular regulatory processes in platelets. In: Colman RW, Hirsh J, Marders VJ, Salzman EW, eds. *Hemostasis and Thrombosis. Basic Principles and Clinical Practice*, 3rd Edn. Philadelphia: JB Lippincott, 1994; 610–613

32 Zwaal RF, Schroit AJ. Pathophysiologic implications of membrane phospholipid asymmetry in blood cells. *Blood* 1997; **89**: 1121–32

33 Magocsi M, Sarkadi B, Kovacs T, Gardos G. Thrombin-induced activation of calcium transport pathways and their role in platelet functions. *Biochim Biophys Acta* 1989; **984**: 88–96

34 Anderson ER, Foulks JG, Godin DV. The effect of local anaesthetics and antiarrhythmics on the responses of rabbit platelets to ADP and thrombin. *Thromb Haemostat* 1981; **45**: 18–23

35 Watala C, Boncler M, Golanski J, Koziolkiewicz W, Walkowiak B, Cierniewski CS. Release of calcium and P-selectin from intraplatelet granules is hampered by procaine. *Thromb Res* 1999; **94**: 1–11

36 DeCandia E, De Cristofaro R, Landolfi R. Thrombin-induced platelet activation is inhibited by high- and low-molecular weight heparin. *Circulation* 1999; **99**: 3308–14

37 Jamnicki M, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. The effect of potato starch derived and corn starch derived hydroxyethyl starch on *in vitro* blood coagulation. *Anaesthesia* 1998; **53**: 638–44

38 Tobias MD, Pilla MA, Rogers C. Effects of sequential hemodilution upon TEG assessed coagulation. *Anesth Analg* 1995; **80**: S503

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Infusion of amino acid enriched solution hastens recovery from neuromuscular block caused by vecuronium

Y. Saitoh[1]*, K. Kaneda[2], Y. Tokunaga[2] and M. Murakawa[1]

[1]Department of Anesthesiology, Fukushima Medical University School of Medicine, Fukushima, Japan and [2]Department of Anesthesiology, Toride Kyodo General Hospital, Ibaraki, Japan

**Corresponding author: Department of Anesthesiology, Fukushima Medical University School of Medicine, Hikarigaoka 1, Fukushima City, Fukushima, 960–1295, Japan*

We investigated the effect of an amino acid infusion on neuromuscular block produced by vecuronium, and on rectal temperature and surface temperature over the adductor pollicis muscle. Sixty adult patients undergoing general anaesthesia were randomly divided into four groups of 15 patients each: amino acid (AA)-post-tetanic count (PTC); AA-train-of-four (TOF); control (C)-PTC; or C-TOF group. In the AA-PTC and AA-TOF groups, after a bolus of vecuronium 0.1 mg kg^{-1}, a continuous infusion of an 18 amino acid enriched solution (AMIPAREN®) was started at a rate of 166 kJ h^{-1}. In the C-PTC and C-TOF groups, normal saline was administered. Time from vecuronium to the return of the PTC in the AA-PTC group was significantly shorter than in the C-PTC group (mean (SD), 13.3 (4.5) versus 18.0 (5.6) min, $P<0.05$). Times to return of T1, T2, T3, and T4 (first, second, third, and fourth twitch of TOF) in the AA-TOF group were significantly shorter than in the C-TOF group (21.1 (4.5) versus 28.0 (8.2) min for T1, $P<0.05$). PTC in the AA-PTC group was significantly greater than in the C-PTC group; 25–35 min after administration of vecuronium ($P<0.05$). T1/T0 and T4/T1 in the AA-TOF group were significantly higher than in the C-TOF group, 40–120 and 50–120 min after vecuronium respectively ($P<0.05$). Rectal temperature and surface temperature over the adductor pollicis muscle in the AA-PTC and AA-TOF groups were significantly higher than in the control groups 50–120 and 100–120 min after vecuronium respectively ($P<0.05$). Infusion of amino acid enriched solution hastens recovery from neuromuscular block.

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Amino acid enriched solution supplies energy to skeletal muscle.[1–5] Branched-chain amino acids (leucine, isoleucine, and valine), in particular, are easily available energy substrates.[1–5] Nissen and colleagues[1] reported that the leucine metabolite, β-hydroxy-β-methylbutyrate caused a significant increase in muscle strength. They suggested that this leucine metabolite prevented or slowed the process of muscle damage and partially preventing the increase in proteolysis associated with intense muscular work. Mourier and colleagues[2] showed that the combination of moderate energy restriction and branched-chain amino acid supplementation induced significant and preferential losses of visceral adipose tissue and allowed maintenance of a high level of performance. It has also been reported that the decrease in body temperature that occurs during general anaesthesia can be attenuated by a continuous infusion of amino acid enriched solution.[3 6–8] This thermal effect is thought to be a result of the supply of energy to skeletal muscle.[3 6–8]

If the temperature over the adductor pollicis is decreased, recovery from neuromuscular block in this muscle is delayed.[9 10] An infusion of amino acid-enriched solution may speed recovery from neuromuscular block because amino acids prevent hypothermia. However, no previous studies have investigated the effect of amino acids on neuromuscular block and temperature over the adductor pollicis muscle during general anaesthesia. In this study, we examined the recovery of post-tetanic count (PTC) and the

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train-of-four (TOF) response, and changes in rectal temperature or surface temperature and the adductor pollicis muscle, during a continuous infusion of amino acid enriched solution in anaesthetized patients receiving vecuronium compared with controls.

Methods

Our local ethics committee approved the procedure of this study and written informed consent was obtained from each patient. Sixty adult patients, ASA I–II, undergoing elective ear nose and throat surgery (tympanoplasty) or ophthalmological surgery (segmental buckling or vitrectomy) lasting 2–4 h under general anaesthesia were enrolled in the study. The patients were randomly divided into four groups of 15 patients each: amino acid (AA)-PTC; AA-TOF; control (C)-PTC; or C-TOF group. No patient had neuromuscular, hepatic, renal, or cardiac disorders or was receiving any drugs known to affect neuromuscular transmission. Up to 21:00 h on the evening before surgery, all patients were allowed to eat and drink freely. Thereafter, they were fasted. Anaesthesia started about 09:00.

Pre-medication consisting of atropine 0.01 mg kg^{-1} and hydroxyzine 1.0 mg kg^{-1} was given i.m. 30 min before induction of anaesthesia. On arriving at the operating theatre, two surface stimulating electrodes were positioned over the ulnar nerve at the wrist. A force displacement transducer was attached to the thumb of one arm.

Infusion of amino acids and monitoring of neuromuscular block

In each group, acetate Ringer's solution was infused i.v. at a rate of 500 ml h^{-1} via an 18-gauge catheter inserted into the cubital vein. In each group, anaesthesia was induced with propofol 2 mg kg^{-1}. After loss of the eyelash reflex, TOF stimuli were applied every 12 s using a nerve stimulator (Myotest DBS, DBS-000E, Biometer International, Odense, Denmark). Four square-wave twitch stimuli of 0.2 ms duration were applied at 2 Hz. The mechanical response of the adductor pollicis muscle was measured using a neuromuscular transmission analyser (Myograph 2000, Biometer International, Odense, Denmark). In each patient, TOF stimuli were delivered at 20, 30, 40, 50, and 60 mA. If a supramaximal response of the thumb was produced at 20, 30, 40, or 50 mA, the stimulating current for the patient was fixed at 50 mA. If the supramaximal response of the thumb could not be produced at 50 mA, the stimulating current for the patient was fixed at 60 mA. The height of the first response of the TOF was regarded as control twitch height (T0). The control value was determined 2–3 min after starting TOF stimuli. During this stabilization period, the patients' lungs were ventilated using a facemask with oxygen 6 litre min^{-1} and isoflurane 1% inspired concentration.

Table 1 Amino acid mixture given i.v. to the patients in the AA-PTC and AA-TOF groups

Amino acid	**Concentration (g 200 ml^{-1})**
Leucine	2.80
Isoleucine	1.60
Valine	1.60
Lysine	2.10
Threonine	1.14
Tryptophan	0.40
Methionine	0.78
Phenylalanine	1.40
Cysteine	0.20
Tyrosine	0.10
Arginine	2.10
Histidine	1.00
Alanine	1.60
Proline	1.00
Serine	0.60
Aminoacetate	20.00
Aspartate	0.20
Glutamate	0.20

A continuous i.v. infusion of a mixture of 18 amino acids (AMIPAREN®, Otsuka Pharmaceutical Inc., Tokyo, Japan) (Table 1) was then started in the AA-PTC and AA-TOF groups at a rate of 100 ml h^{-1}, corresponding with 166 kJ h^{-1} of energy, using a syringe pump (Terufusor, TE-312, Terumo Inc., Tokyo, Japan). The infusion rate was determined according to the AMIPAREN® data sheet. Thereafter, vecuronium 0.1 mg kg^{-1} was administered i.v. to facilitate tracheal intubation. In the C-PTC and C-TOF groups, the degree of neuromuscular block was monitored in the same manner as in the AA-PTC and AA-TOF groups and vecuronium 0.1 mg kg^{-1} was injected to facilitate tracheal intubation. Normal saline was infused continuously at a rate of 100 ml h^{-1} instead of the infusion of the amino acid enriched solution. All i.v. fluids were at room temperature. A warming mattress (Medi-Therm, MTA-4700, Gaymar Industries Inc., New York, NY, USA) had been laid on the operating bed, and the temperature of the warm water in the warming mattress was kept at 37°C. The monitored arm was covered with towels. The room temperature was 27–28°C.

After administration of vecuronium in the AA-PTC and C-PTC groups, PTC was measured every 5 min. A 50 Hz tetanic stimulus was delivered at 50 or 60 mA for 5 s, and after a pause of 3 s, 20 single twitch stimuli of 0.2-ms duration square-waves were given every 1 s at 50 or 60 mA. The number of detectable muscular contractions in response to the single twitch stimuli was regarded as the PTC. The times from the vecuronium injection to the return of a PTC of 1 (only one response to the 20 single twitch stimuli could be elicited) were compared between the AA-PTC and C-PTC groups. In addition, in the two groups, time courses of recovery of PTC were compared.

In the AA-TOF and C-TOF groups, TOF stimuli were applied every 12 s at 50 or 60 mA. The times from vecuronium to the return of T1, T2, T3, and T4 (the first, second, third, and fourth response in TOF) were compared between the two groups. T1/T0 and T4/T1 were recorded every 10 min, and were also compared between the AA-TOF and C-TOF groups.

Measurement of rectal temperature and surface temperature over adductor pollicis muscle

About 5 min before induction of anaesthesia, a thermometer probe was inserted 10–15 cm into the rectum and the rectal temperature was monitored on an anaesthesia monitoring system (Anesthesia System/3, AS/3, Datex-Ohmeda Division Instrumentarium Corp. Inc., Helsinki, Finland). A surface skin thermometer probe (Terumo-Finer, CTM-303, Terumo Inc., Tokyo, Japan) was positioned over the adductor pollicis muscle in each patient.

Control rectal temperature and temperature over the adductor pollicis muscle were recorded. From the beginning of the infusion of the amino acid enriched solution, the two temperatures were noted every 10 min. The rectal temperatures recorded in the AA-PTC and AA-TOF groups were compared with that evaluated in the C-PTC and C-TOF groups. Similarly, the temperature over the adductor pollicis muscle in the AA-PTC and AA-TOF groups was compared with that in the C-PTC and C-TOF groups every 10 min.

Anaesthetic management

In each group, anaesthesia was maintained with nitrous oxide 66% in oxygen and 0.5% end-tidal isoflurane. A bolus dose of fentanyl 2 μg kg^{-1} was administered i.v. If the depth of anaesthesia was thought to be insufficient, a further bolus dose of fentanyl 2 μg kg^{-1} was given. Ventilation was controlled to maintain normocapnia ($P\mathrm{E}'_{CO_2}$ 4.1–5.0 kPa). The anaesthetic concentrations and $P\mathrm{E}'_{CO_2}$ were measured continuously using a multiple gas monitor (Capnomac Ultima, S-31-03, Datex Inc., Helsinki, Finland).

Statistical analyses

All results are expressed as number or mean (SD). Patient characteristics were compared among the four groups using analysis of variance (ANOVA) and Scheffe's multiple comparison. The times to return of PTC1 between the AA-PTC and C-PTC groups were compared using the unpaired *t*-test. Similarly, times to return of T1, T2, T3, or T4 were compared between the AA-TOF and C-TOF groups using the unpaired *t*-test. Comparison of time courses of recovery of PTC between the AA-PTC and C-PTC groups was made using Kruskal–Wallis test followed by Mann–Whitney *U*-test with Bonferroni's adjustment. The time courses of recovery of T1/T0 and T4/T1 were compared between the AA-TOF and C-TOF groups using ANOVA followed by unpaired *t*-test with Bonferroni's adjustment. The comparison of the changes in rectal temperature between the AA-PTC and AA-TOF groups, and the C-PTC and C-TOF groups, and the comparison of the changes in the temperature over the adductor pollicis muscle between the AA-PTC and AA-TOF groups and the C-PTC and C-TOF groups were made using ANOVA followed by the unpaired *t*-test with Bonferroni's adjustment. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using a statistical package (SYSTAT 8.0, SPSS Inc., Chicago, IL, USA) running on a personal computer.

Results

Patient characteristics were comparable among the four groups (Table 2). In all patients, a supramaximal response of the adductor pollicis muscle could be elicited at 30, 40, or 50 mA. The nerve stimuli were therefore applied at 50 mA in all patients.

Table 2 Patient characteristics in the AA-PTC, C-PTC, AA-TOF, and C-TOF groups. Values are number or mean (SD). No significant differences were observed among the four groups. AA=amino acid, C=control, PTC=post-tetanic count, TOF=train-of-four

Group	AA-PTC	C-PTC	AA-TOF	C-TOF
Number	15	15	15	15
Sex (M/F)	6/9	6/9	6/9	6/9
Age (yr) [range]	55 (12) [23–74]	62 (9) [30–78]	57 (10) [31–79]	54 (10) [38–77]
Height (cm)	157 (11)	155 (10)	159 (9)	158 (10)
Weight (kg)	55 (12)	62 (9)	59 (10)	58 (9)

Table 3 Times from administration of vecuronium 0.1 mg kg^{-1} to the return of PTC1 in the AA-PTC and C-PTC groups, and to return of T1, T2, T3, and T4 in the AA-TOF and C-TOF groups. Values are mean (SD). Times to return of PTC1 in the AA-PTC groups were significantly shorter than in the C-PTC groups ($P<0.05$). Times to the return of T1, T2, T3, and T4 in the AA-TOF group were significantly shorter than in the C-TOF group ($P<0.05$). AA=amino acid, C=control, PTC=post-tetanic count, TOF=train-of-four

Group	AA-PTC AA-TOF	C-PTC C-TOF	*P* value
PTC1 (min)	13.3 (4.5)	18.0 (5.6)	0.018
T1 (min)	21.1 (4.5)	28.0 (8.2)	0.008
T2 (min)	28.7 (6.7)	37.8 (9.4)	0.005
T3 (min)	33.3 (7.2)	44.9 (11.7)	0.006
T4 (min)	35.1 (7.4)	46.7 (11.6)	0.003

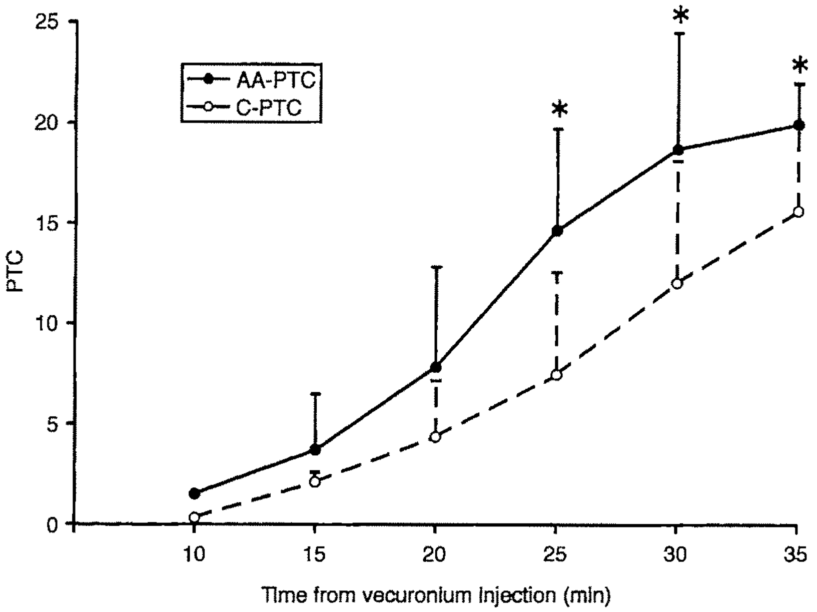

Fig 1 Recovery of PTC in the AA-PTC and C-PTC groups. Values are mean (SD). *$P<0.05$ between the groups. AA=amino acid, C=control, PTC=post-tetanic count.

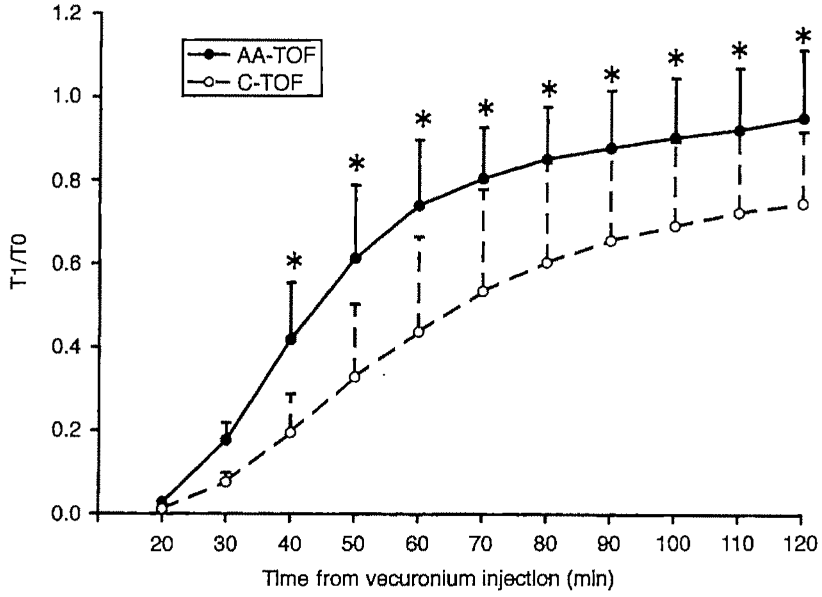

Fig 2 Recovery of T1/T0 in the AA-TOF and C-TOF groups. Values are mean (SD). *$P<0.05$ between the groups. AA=amino acid, C=control, TOF=train-of-four.

Time from vecuronium injection to the return of PTC1 in the AA-PTC group was significantly shorter than in the C-PTC groups ($P<0.05$). Also, times to the return of T1, T2, T3, and T4 in the AA-TOF group were significantly shorter than in the C-TOF group ($P<0.05$) (Table 3).

PTC in the AA-PTC group was significantly higher than in the C-PTC groups 25–35 min after administration of vecuronium ($P<0.05$) (Fig. 1). T1/T0 and T4/T1 in the AA-TOF group were significantly higher than in the C-TOF group 40–120 and 50–120 min after administration of vecuronium respectively ($P<0.05$) (Figs 2 and 3).

At the final time point, 120 min after administration of vecuronium, in the AA-TOF and C-TOF groups, T1/T0 was 0.95 (0.16) [0.73–1.30] and 0.75 (0.16) [0.38–1.01] (mean (SD) [range]) respectively. In five patients in the AA-TOF group, T1/T0 returned to greater than 1.0. Similarly, 120

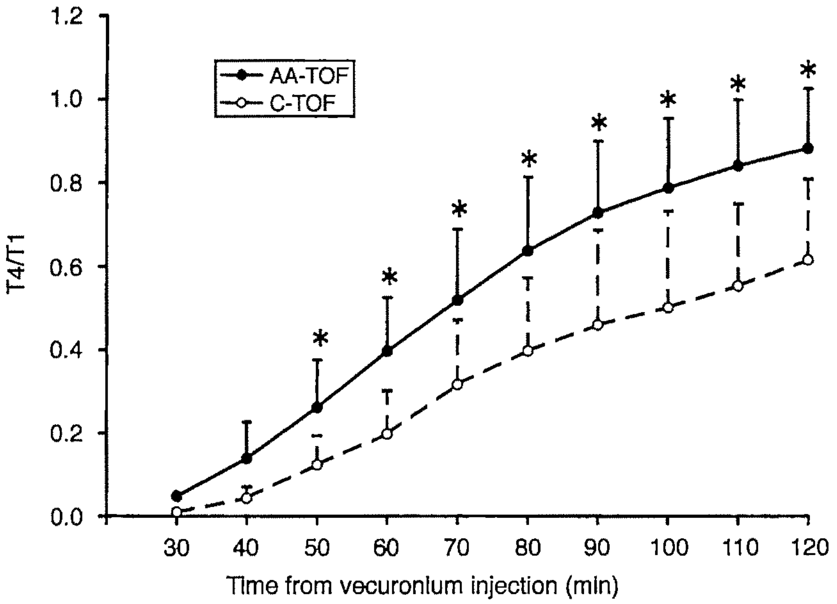

Fig 3 Recovery of T4/T1 in the AA-TOF and C-TOF groups. Values are mean (SD). $^*P<0.05$ between the groups. AA=amino acid, C=control, TOF=train-of-four.

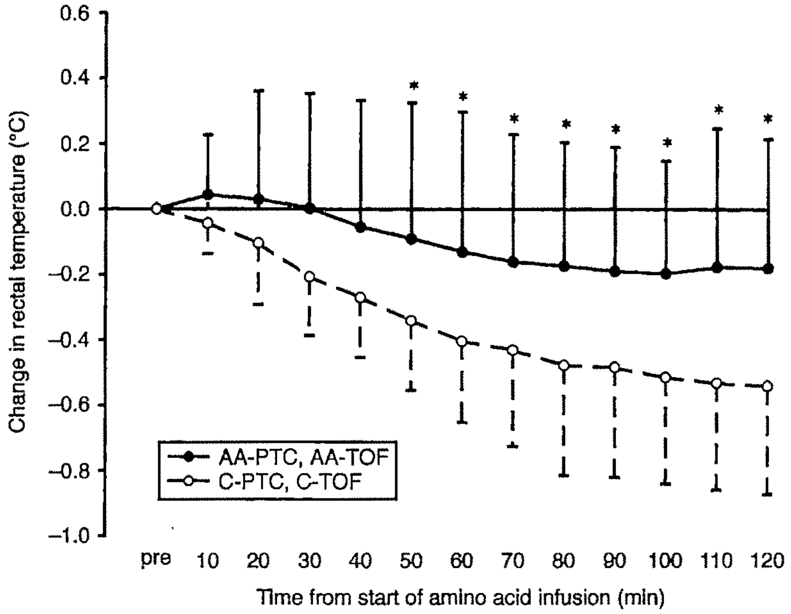

Fig 4 Changes in rectal temperature from baseline during anaesthesia in patients in the AA-PTC and AA-TOF groups receiving amino acid enriched solution and in patients in the C-PTC and C-TOF groups receiving amino acid free solution. Values are mean (SD). $^*P<0.05$ between the groups. AA=amino acid, C=control, PTC=post-tetanic count, TOF=train-of-four.

min after administration of vecuronium, in the AA-TOF and C-TOF groups, T4/T1 was 0.88 (0.12) [0.57–1.00] and 0.61 (0.19) [0.33–0.92] (mean (SD) [range]) respectively.

Before induction of anaesthesia, the rectal temperature in the AA-PTC and AA-TOF groups and that in the C-PTC and C-TOF groups did not significantly differ (36.8 (0.3) versus 37.0 (0.6)°C, NS). Similarly, before induction of anaesthesia, the temperature over the adductor pollicis muscle in the AA-PTC and AA-TOF groups was comparable with that in the C-PTC and C-TOF groups (33.1 (1.3) *vs* 32.9 (1.1)°C, NS). Rectal temperature decreased by approximately 0.2 and 0.5°C respectively in patients receiving an amino acid infusion or controls during the study period of 120 min. Rectal temperature in patients receiving an amino acid

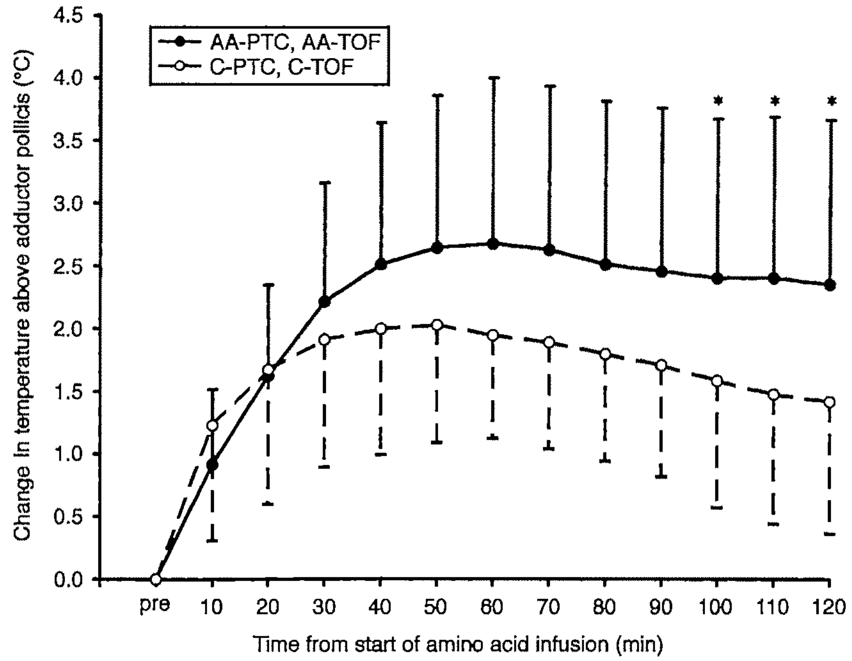

Fig 5 Changes in temperature over the adductor pollicis muscle from baseline throughout anaesthesia in patients in the AA-PTC and AA-TOF groups receiving amino acid enriched solution and in patients in the C-PTC and C-TOF groups receiving amino acid free solution. Values are mean (SD). *$P<0.05$ between the groups. AA=amino acid, C=control, PTC=post-tetanic count, TOF=train-of-four.

infusion became stable about 80–100 min after starting the administration of amino acid. In contrast, rectal temperature in patients in the control groups continued to decrease gradually during the study period. The peripheral temperature over the adductor pollicis muscle increased by about 2.7 and 2.0°C in patients receiving amino acids and in the control group respectively. The increases in the peripheral temperature in patients receiving amino acids and in the control group were rapid for the first 30 min, became stable within about 40–60 min. The decrease in the rectal temperature was less and the increase in the surface temperature over the adductor pollicis muscle was greater in the AA-PTC and AA-TOF groups than in the C-PTC and C-TOF groups 50–120 and 100–120 min after the beginning of administration of amino acid enriched solution respectively ($P<0.05$) (Figs 4 and 5).

In no patient did the rectal or peripheral temperature over the adductor pollicis muscle decrease to less than 35.6 or 30.2°C respectively. In two and four patients in the amino acid groups and control groups respectively, when vecuronium was given, the peripheral temperature over the adductor pollicis muscle was less than 32°C. However, in these patients, 10 min after vecuronium, the peripheral temperature over the adductor pollicis muscle had increased to more than 32°C.

Discussion

This study indicates that a continuous infusion of amino acid enriched solution speeds recovery from vecuronium-induced neuromuscular block in anaesthetized patients. During continuous administration of the amino acid enriched solution, the times from vecuronium to the return of PTC1, T1, T2, T3, and T4 were shortened. Also, the rates of recovery of the PTC, T1/T0, and T4/T1 was hastened. The decreases in rectal temperature in the AA-PTC and AA-TOF groups were significantly less than those in the C-PTC and C-TOF groups. The increases in temperature over the adductor pollicis muscle in the AA-PTC and AA-TOF groups were significantly greater than those in the C-PTC and C-TOF groups.

Amino acids are readily available energy substrates for skeletal muscle.[1–5] Several studies have demonstrated amino acid-induced thermogenesis in patients during general anaesthesia.[3] [6–8] The infusion of amino acid enriched solution prevents hypothermia.[4–8] It has been postulated that amino acid-induced heat production is mainly a result of the delivery of energy substrates to skeletal muscle.[3] [6] Approximately 75% of amino acid-induced thermogenesis during anaesthesia seems to be produced here.[3] [6]

The amino acid-induced thermic effect is more apparent in patients under general anaesthesia than in awake subjects.[6] [11] The reason for this is unknown. It has been reported that most anaesthetic agents considerably reduced whole body oxidative metabolism and hence the production of heat.[7] For example, volatile anaesthetics directly depress protein synthesis and induce hypothermia.[6] Amino acid enriched solution may reverse the cooling effect of the volatile agents.

Mourier and colleagues[2] reported that even when wrestlers were subjected to moderate energy restriction, branched-chain amino acid supplementation allowed maintenance of a high level of sports performance. Similarly, Nissen and colleagues[1] demonstrated that the leucine metabolite, β-hydroxy-β-methylbutyrate, produced a significant increase in muscle strength. The amino acid-induced thermic effect may be related to this increase in muscle strength. The solution increased muscle strength may also prevent the hypothermia.

This study showed that the amino acid-induced effect on recovery of neuromuscular block had a very rapid onset. For example, the mean time from vecuronium injection to the return of PTC1 in the C-PTC group was 18.0 min, but in the AA-PTC group was only 13.3 min. Also, Selldén and Lindahl[6] and Selldén and colleagues[7] have reported that during general anaesthesia, the body temperature in patients who were given the amino acid enriched solution becomes significantly higher than that in patients who did not receive it within 20 min.

In previous studies,[6 8] rectal temperature decreased by approximately 0.5°C and 1.0–1.5°C respectively during general anaesthesia in patients receiving an amino acid infusion or controls. In contrast, in this study, the maximum decreases in the rectal temperature were only 0.2 and 0.5°C respectively. We are not able to explain the reason for this difference. However, El-Gamal and colleagues[12] reported that an operating room temperature around 26°C is effective in preventing a decrease in core temperature during general anaesthesia. In this study, the operating room temperature was 27–28°C, in contrast with 20–23°C in the previous studies.[6 8]

It has been noted that if the temperature over the adductor pollicis muscle is less than 32°C, recovery of neuromuscular block is delayed.[9 10] Hypothermia is associated with a decrease in acetylcholine release.[9 10] The present results may be because of in part the prevention of hypothermia at the adductor pollicis muscle. But in two patients in the AA-PTC and AA-TOF groups and four in the C-PTC and C-TOF groups, when vecuronium was given, the peripheral temperature over the adductor pollicis muscle was less than 32°C. Accordingly, in these patients, recovery of neuromuscular block might have been delayed. However, by 10 min after vecuronium, the peripheral temperature over the adductor pollicis muscle had increased to more than 32°C in these patients.

In this study, the peripheral temperature over the adductor pollicis muscle increased by about 2.7 and 2.0°C in patients receiving amino acids and in the control group respectively. In all patients, the peripheral temperature became stable within 40–60 min. These results were comparable with the findings of Sessler and colleagues,[13] although in their study, the increase in the surface skin temperature over the hand was greater than 4°C. They noted that the increase in the surface skin temperature was a result of the redistribution of heat from the warm central compartment to cooler peripheral tissues.

Neuromuscular monitoring was started after loss of the eyelid reflex, but 1% isoflurane was then used for maintenance of anaesthesia for the 2 or 3 min before control readings of the TOF were taken. The use of isoflurane might have affected the neuromuscular response. However, it has been reported that 10 min exposure to isoflurane is insufficient to affect spontaneous recovery from mivacurium.[14] We do not think that in this study any isoflurane-induced effect was of clinical importance.

All patients were pre-medicated with atropine 0.01 mg kg^{-1}. Atropine inhibits the activity of sweat glands, and the skin becomes hot and dry. Brown[15] noted that sweating may be depressed sufficiently to raise the body temperature, although only after large doses of atropine are given.[15] Although Brown[15] did not define the dose of atropine that caused hyperthermia, he noted that therapeutic doses of 0.5–1.0 mg did not do so.

References

1 Nissen S, Sharp R, Ray M, *et al.* Effect of leucine metabolite β-hydroxy-β-methylbutyrate on muscle metabolism during resistance-exercise training. *J Appl Physiol* 1996; **81**: 2095–104

2 Mourier A, Bigard AX, de Kerviler E, *et al.* Combined effects of caloric restriction and branched-chain amino acid supplementation on body composition and exercise performance in elite wrestlers. *Int J Sports Med* 1997; **18**: 47–55

3 Selldén E, Bränström R, Brundin T. Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extra-splanchnic tissues. *Clin Sci* 1996; **91**: 431–9

4 Mero A. Leucine supplementation and intensive training. *Sports Med* 1999; **27**: 347–58

5 Freund H, Yoshimura N, Lunetta L, Fisher JE. The role of the branched-chain amino acids in decreasing muscle catabolism in vivo. *Surgery* 1978; **83**: 611–8

6 Selldén E, Lindahl SGE. Postoperative nitrogen excretion after amino acid-induced thermogenesis under anesthesia. *Anesth Analg* 1998; **87**: 641–6

7 Selldén E, Brundin T, Wahren J. Augmented thermic effect of amino acids under general anaesthesia: a mechanism useful for prevention of anaesthesia-induced hypothermia. *Clin Sci* 1994; **86**: 611–8

8 Selldén E, Bränström R, Brundin T. Preoperative infusion of amino acids prevents postoperative hypothermia. *Br J Anaesth* 1996; **76**: 227–34

9 Eriksson LI, Viby-Mogensen J, Lennmarken C. The effect of peripheral hypothermia on a vecuronium-induced neuromuscular block. *Acta Anaesthesiol Scand* 1991; **35**: 387–92

10 Eriksson LI, Lennmarken C, Jensen E, Viby-Mogensen J. Twitch tension and train-of-four ratio during prolonged neuromuscular monitoring at different peripheral temperatures. *Acta Anaesthesiol Scand* 1991; **35**: 247–52

11 Brundin T, Wahren J. Effects of iv amino acids on human splanchnic and whole body oxygen consumption, blood flow and blood temperatures. *Am J Physiol* 1994; **266**: 396–402

12 El-Gamal N, El-Kassabany N, Frank SM, *et al.* Age related thermoregulatory differences in a warm operating room

environment (approximately 26°C). *Anesth Analg* 2000; **90**: 694–8

13 Sessler DI, McGuire J, Moayeri A, *et al.* Isoflurane-induced vasodilation minimally increases cutaneous heat loss. *Anesthesiology* 1991; **74**: 226–32

14 Jalkanen L, Meretoja OA. The influence of the duration of isoflurane anaesthesia on neuromuscular effects of mivacurium. *Acta Anaesthesiol Scand* 1997; **41**: 248–51

15 Brown JH. Atropine, scopolamine, and related antimuscarinic drugs. In: Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn. New York: Pergamon Press, 1990; 150–65

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What can be expected from risk scores for predicting postoperative nausea and vomiting?

C. C. Apfel*, P. Kranke, C.-A. Greim and N. Roewer

Department of Anaesthesiology, University of Würzburg, Josef-Schneider-Str. 2, D-97080 Würzburg, Germany

**Corresponding author*

Several risk scores have been developed to calculate the *probability* of postoperative nausea and vomiting (PONV). However, the power to discriminate which *individual* will suffer from PONV is still limited. Thus, we wondered how the number of predictors in a score affects the discriminating power and how the characteristics of a population—which is needed to measure the power of a score—may affect the results. For ethical reasons and to be independent from centre specific populations, we developed a computer model to simulate virtual populations. Four populations were created according to number, frequency, and odds ratio of predictors. Population I: parameters were derived from a previously published paper to verify whether calculated and reported values are in accordance. Population II: a gynaecological population was created to investigate the impact of the study setting. Populations III and IV: to meet ideal assumptions a model with up to seven predictors with an odds ratio of 2 and 3 was tested, respectively. The discriminating power of a risk score was measured by the area under a receiver operating characteristic curve (AUC) and an increase of more than 0.025 per predictor was considered to be clinically relevant. The AUC of population I was similar to those reported in clinical investigations (0.72). The study setting had a considerable impact on the discriminating power since the AUC decreased to 0.65 in a gynaecological setting. The AUC with the 'idealized' populations III and IV was at best in the range of 0.7–0.8. The inclusion of more than five predictors did not lead to a clinically relevant improvement. The currently available simplified risk scores (with four or five predictors) are useful both as a method to estimate individual risk of PONV and as a method for comparing groups of patients for antiemetic trials. They are also superior to single predictor models which are just using the patients' history of PONV or female gender alone. However, our analysis suggests that the power to discriminate which *individual* will suffer from PONV will remain imperfect, even when more predictors are considered.

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The incidence of post-operative nausea and vomiting (PONV) is still about 25–30%.[1] Thus, innumerable studies have been carried out to investigate prophylactic antiemetic treatments.[2] Meta-analyses have shown that efficacy of prophylactic antiemetic strategies is limited and that the number-needed-to-treat (NNT) to prevent one patient from PONV is at best in the range of 5 when the basal event rate is high.[3–5] In addition, prophylactic compared with therapeutic antiemetic treatment does not improve patient satisfaction unless a high basal event rate is present.[6] Thus, prophylactic antiemetics appear only justified in patients at increased risk for PONV.[7 8]

In the past, high-risk patients were intuitively classified by reference to the past medical history of PONV or the type of surgery. Recently, risk scores have provided an objective risk assessment for PONV.[9–11] Several studies have shown that the risk assessments derived from such scores are robust enough to be also valid both in other hospitals and under different conditions.[11–14] However, the power to discriminate which *individual* will suffer from PONV remains limited (discriminating power). Thus, some centres are starting to develop more complex scores,[15] hoping to gain better results by the inclusion of more predictors. Unfortunately, the development and the validation of such scores requires a

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large number of patients not receiving prophylactic antiemetics which may be ethically questionable if they are at high risk according to current risk scores. Thus, for ethical reasons and to be independent from centre specific populations, we created virtual populations to explore what can be expected from risk scores for predicting PONV by investigating how the number of risk factors and different study settings may affect their discriminating power.

Methods

The virtual populations were created using a computer model as described in more detailed in the appendix.

Population I was created to verify that this model of a virtual population (when based on parameters taken from a previous study on real patients) leads to similar results when compared with the previously reported area under the receiver operating characteristic curve (AUC) from the 'real world'.[11] This was achieved by considering the frequencies and odds ratio (OR) from the previous publication. Then, risk scores considering female gender alone, non-smoking, history of motion sickness or PONV (MSPONVhist), plus post-operative opioids and plus the consideration of the interaction of male gender and MSPONVhist were created (Tables 1 and 2). Its discriminating power was measured by the AUC.

To investigate how the AUC might be affected by a different study setting, a gynaecological setting (population II) was constructed so that female gender could no longer be used as a predictor. The population also included type of operation to quantify the benefit of an additional predictor as most scores were unable to identify the type of operation as an independent risk factor. For this, we were assuming that gynaecological laparoscopies are associated with an OR of 2.3, as previously described.[16]

Finally, for populations III and IV, risk scores considering 1–7 idealized predictors (frequency 50% and OR 2 and 3, respectively) were applied to approximate what can *at best* be expected from an *n*-predictor model (Tables 1 and 2). In summary, four populations with different characteristics were created (Table 1 and 2).

- Population I: Incidence of PONV, frequency, and OR of the predictors were taken from a previous study based on real patients.[11]
- Population II: Incidence, frequency, and OR were modified to represent a gynaecological setting.
- Population III: Incidence of PONV=50%, frequency of risk factors=50%, OR=2.0.
- Population IV: Incidence and frequency as simulation III, but OR=3.0

Characteristics to create the populations were derived from the literature. A systematic review of studies investigating predictors using logistic regression models revealed two publications analysing postoperative vomiting (POV),[13 17] and six analysing PONV.[9–11 15 16 18] One study from a pharmaceutical company was excluded,[18] because individual predictors (e.g. patients history of PONV) were not appropriately considered. A second study was not considered[15] for reasons described in a joint letter from the UK, Finland, and Germany.[19] The remaining studies with more than 1000 patients[10 11 13 16 17] reported ORs for female gender in the range of about 3 while the OR of the other predictors were in the range of 2 or less. Thus, the first assumption was that the OR of clinically relevant predictors for PONV are at best in the range of 2–3.

While some scores allow exact calculations of the probability using the coefficients derived from the logistic

Table 1 Frequency of PONV and predictors in the different populations

Population I (%)	Population II (%)	Population III (%)	Population IV (%)
PONV=34.5	PONV=60	PONV=50	PONV=50
Females=56.9	Females=100	1st Predictor=50	1st Predictor=50
Non-smoker=73.1	Non-smoker=80	2nd Predictor=50	2nd Predictor=50
MS-PONVhist=35.1	MS-PONVhist=50	3rd Predictor=50	3rd Predictor=50
Post-operative opioids=45.8	Post-operative opioids=50	4th Predictor=50	4th Predictor=50
Interaction=7.6	Laparoscopies=25	5th Predictor=50	5th Predictor=50
–		6th Predictor=50	6th Predictor=50
–		7th Predictor=50	7th Predictor=50

Table 2 OR of predictors in the different populations

Population I	Population II	Population III	Population IV
Females=3.57	Females=3.57	1st Predictor=2.0	1st Predictor=3.0
Non-smoker=2.05	Non-smoker=2.05	2nd Predictor=2.0	2nd Predictor=3.0
MS-PONVhist=1.92	MS-PONVhist=1.92	3rd Predictor=2.0	3rd Predictor=3.0
Post-operative opioids=2.18	Post-operative opioids=2.18	4th Predictor=2.0	4th Predictor=3.0
Interaction=2.14	Laparoscopies=2.3	5th Predictor=2.0	5th Predictor=3.0
–		6th Predictor=2.0	6th Predictor=3.0
–		7th Predictor=2.0	7th Predictor=3.0

models[9 13 17] two recent studies provided evidence that a simplification by just considering the number of binary predictors does not significantly impair the discriminating power and still provides an appropriate estimate of the individuals risk.[10 11] This led to the second assumption: that considering binary variables does not significantly alter the results.

Palazzo and Evans found an interaction between gender and history of PONV.[9] This was also found in a cross-validation between two centres but detailed analysis revealed this effect to be negligible.[11] Because the other studies[10 13] did not find any other relevant interactions, the third assumption is that an interaction (covariation) between risk factors for PONV is negligible.

The discriminating power of a score was measured by the area under the receiver operating characteristic (ROC)-curve (AUC) as previously described.[10 11 13–15 17] When the average risk of PONV is 25% and the score results in a probability of 25% for almost every patient, then it would be impossible to discriminate *individuals* in that population who will suffer from those who will not. If, in contrast, 75% of the patients are predicted to have a relatively low risk while the remaining 25% will be predicted with a relatively high risk, then the score may predict PONV correctly in most of the *individuals*, for example, with acceptable discriminating power. Details on the calculation and interpretation of the discriminating power—which considers the relationship between sensitivity and specificity in the ROC-curve—are described elsewhere.[20 21]

For practical reasons, an increase in the AUC of 0.025 per additional risk factor is considered as clinically relevant. This is roughly associated with a 5% higher sensitivity at a specificity of 50%. As this modelling is based on virtual populations, confidence intervals or calculations of P-values are not appropriate.

Results

In population I, a single predictor model resulted in AUCs of about 0.60. Female gender (AUC=0.64) had a greater impact than non-smoking (AUC=0.57), history of motion sickness or PONV (0.58) or post-operative opioids (0.60) because of the high OR of 3.6 and the frequency or approximately to 50% (Fig. 1). The four-predictor model resulted in a clinically relevant higher AUC of 0.72 (Figs 1 and 2) which is similar to the average AUC of the cross-validated scores from a previous publication.[11] When an additional predictor (e.g. interaction between male gender and MSPONVhist) is considered (Fig. 2, upper graph), no clinically relevant improvement is noticeable (ΔAUC<0.01).

When such a score is applied to the gynaecological setting (population II) female gender did not contribute to the discriminating power of the score (AUC=0.5). Consideration of the other three predictors leads to an AUC of 0.65 (Fig. 2, lower graph). However, further predictors (e.g. laparoscopy with an OR of 2.3) did not improve discriminating power significantly (ΔAUC<0.025, Fig. 2).

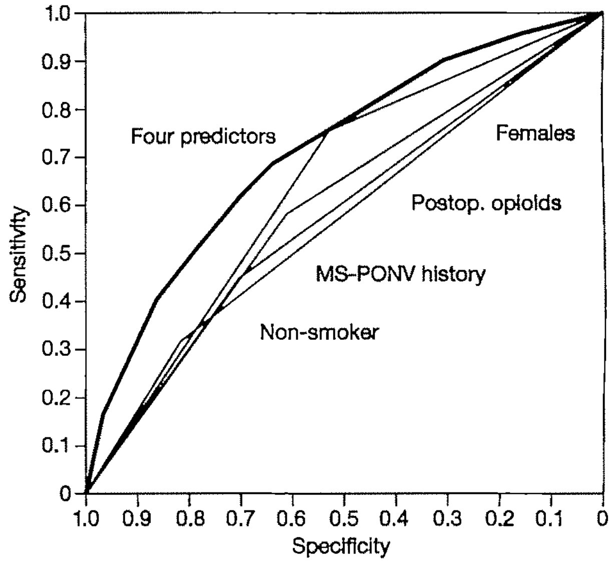

Fig 1 ROC-curve for the single predictor models and for the four-predictor model. The single predictor model considered either female gender, non-smoking, history of motion sickness or PONV and post-operative opioids while the four-predictor model considered all predictors simultaneously. Note, that the four-predictor model had a clinically relevant larger AUC than any single predictor model.

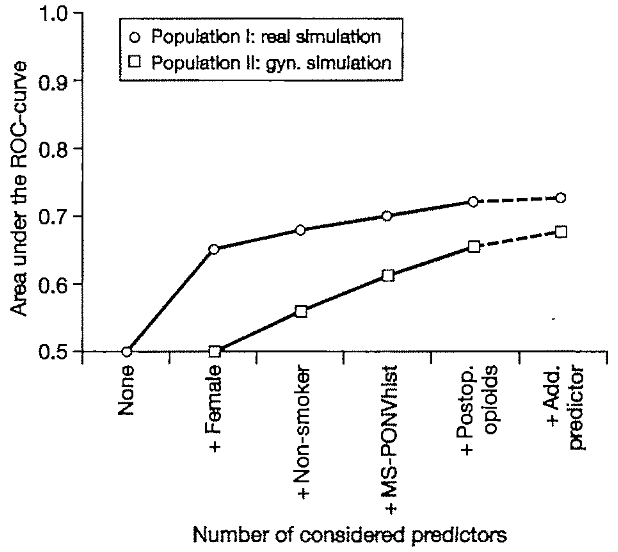

Fig 2 (Upper curve) AUC for population I, for example, when all parameters were taken from a previous study.[11] The interval indicated by the vertical lines displays the range of the published AUC when four or five predictors were applied to its original data set. (Lower curve) AUC for population II, for example, when this score is applied to a gynaecological setting. Note, that considering the additional predictor such as 'laparoscopy' does not lead to a clinically relevant improvement. The dotted lines indicate that the increase of the AUC per additional predictor is less than 0.025. MS-PONV hist=history of motion sickness or PONV. ROC-curve=receiver operating characteristic-curve.

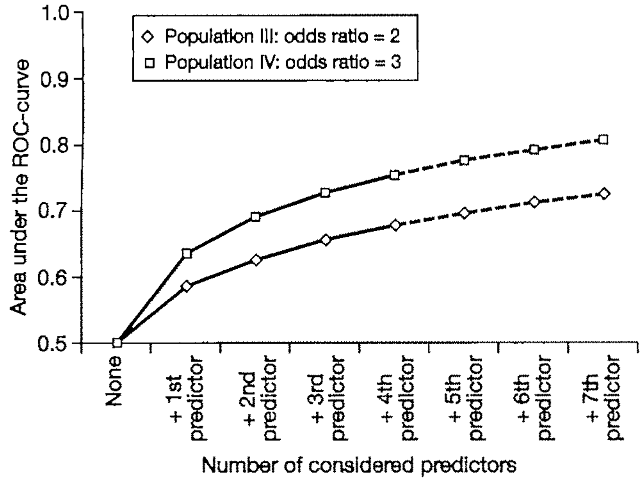

Fig 3 (Lower curve) AUC for population III, for example, all predictors were assumed to have an OR of 2. (Upper curve) AUC for population IV, for example, all predictors were assumed to have an odds ratio of 3. Note, that a four-predictor model is much better than a single factor prediction. However, from four or five factors onwards, the clinical relevance becomes questionable as the increase of the area under the curve per additional predictor becomes less than 0.025, as indicated by the dotted lines. ROC-curve=receiver operating characteristic-curve.

The area of the ROC-curves for populations III and IV, when 0–7 risk factors are considered, are depicted in Figure 3. Again, the improvement in discriminating power is most obvious when the first predictor is introduced and decreases with every additional factor. The data demonstrate that four predictors are clearly superior to a single predictor model (ΔAUC ~0.12) but the increase of the AUC with any further risk factor becomes less than 0.025.

Discussion

This virtual population model appeared to allow centre independent investigations to quantify the relative impact of risk factors on the discriminating power of scores for predicting PONV. It could be shown that the prediction with several risk factors is superior to a prediction with a single factor (e.g. female gender or the history of PONV) and resulted in an AUC of ~0.72. This corresponds to a sensitivity and specificity of about 75 and 50%, respectively. Therefore, we recommend the use of one of the simplified multifactorial models[10 11] for an individual risk assessment in daily practice. Further, these scores should be used for group comparisons in antiemetic trials as the impact of several non-significant risk factors may well add up to a clinically significant different baseline risk.[22] Although, their predictive ability remain imperfect, the suggested models (considering real and ideal parameters from current data of the literature) give little reason to assume that future models will lead to significantly better predictions unless other risk factors with much higher ORs are discovered and confirmed by several centres.

Population I, created from parameters of a previously published population, resulted in a discriminating power, as expressed by the area under the receiver operating characteristic curve (AUC), of 0.72 when four predictors were considered. This is in the range of 0.683–0.746 when a score was applied to its original centre.[11] As the discriminating power of the risk scores is comparable when applied to the virtual and the real population, we conclude that this model is a good representative of reality. Although the characteristics to create the virtual population were identical to the real population, other underlying characteristics were of course not considered. If, for example, a relatively strong, up to now, undiscovered predictor was unevenly distributed in the real but not in the virtual population, the discriminating power may have resulted in lower AUC in the real compared with the virtual population. Thus, it was reassuring that the AUC applied to the virtual population was in the expected range. Further, it could be shown that female gender as the sole predictor already has an AUC of 0.64, but this can be improved to 0.72, when three additional predictors are considered. However, any further predictor, such as an interaction between male gender and MSPONVhist, did not lead to a significant improvement (ΔAUC <0.025). For clinical purposes a score needs to be easy applicable and as addition of further risk factors may complicate calculations for little improvement in risk assessment, the benefit of introducing a further predictor needs to be justified.

To investigate the potential impact of a different study setting on the discriminating power of a score, we constructed the most extreme deviation from the original, which is a gynaecological setting. This would eliminate the benefit of the strongest predictor (population II). The discriminating power with the remaining three predictors was 0.65. This lower discrimination was to be expected. It is noteworthy that in an investigation of a very homogeneous population, for example, all patients are female non-smokers with MSPONVhist undergoing procedures, which most likely will require post-operative opioids, a score based on those predictors will probably calculate for every patient a risk of 79%.[11] As all patients will have the same risk, the score will not be able to discriminate between expected vomiters or non-vomiters, for example, AUC will be 0.5. This does not necessarily mean that the score is useless in that setting as it may still indicate that all these patients have a very high risk for PONV, which could justify the use of prophylactic antiemetics. This example demonstrates that the discriminating power of a scoring system may be affected by the investigated population and that the calibration curve is another important descriptor which can not be analysed with this model. In this respect, some validation studies may be needed to provide acceptable calibration curves in other centres. Interestingly, the risk models which have been validated from other centres[10 11] were independent of the type of operation as its relative impact was negligible. To the best of our knowledge, there seem to be only two valid studies in which the type of operation led to statistically significant OR in multivariate analyses.[13 16] However, their results are controversial and a score considering the operation did not lead to a better prediction compared with the previously described operation-independent model.[13] Although there is little evidence supporting the widespread notion that the type of surgery is a strong risk factor, we tested this hypothesis. Given that 25% of gynaecological patients will undergo laparoscopic surgery with an OR of 2.3,[16] this improvement of about 0.02 led to an AUC of 0.67 which does not appear to be clinically relevant.

The best results can be expected if the frequency of PONV is 50% and if the frequencies of the predictors are also 50%. As pointed out, the overall OR can at best be assumed to be in the range of 2–3.[10 11 16 17] These assumptions were considered in the virtual populations III and IV and resulted in AUCs in the range of 0.72 up to 0.8 which support the previously established models reporting AUCs between 0.71[10] and 0.78[17] in real populations. Again, further inclusion of more than four or five risk factors does not lead to a clinically relevant increase in the discriminating power in the population models as found by Koivuranta and coworkers who reported an AUC of 0.721 in an eight factors and 0.710 in a five factor model.

Creating a virtual population led to practically identical results to those reported from real populations. The discriminating power of risk scores for predicting PONV can at best be expected to be in the range of 0.7–0.8 which means that the discrimination of *individuals* who will suffer from those who will not is still imperfect and will not significantly improve with further predictors. Unless there is consistent evidence that other predictors with a much stronger impact do exist, it is unlikely that future risk scores will provide a significantly better prediction for PONV. Thus, for the time being, it may be ethically questionable to develop new risk scores based on a large number of patients known to be at high risk who would be deprived of an effective prophylactic antiemetic strategy.

Appendix

Creation of the virtual population

For each predictor the coefficients were calculated by taking the logarithm of the OR. Up to seven predictors were considered in a model so that 2^7=128 combinations are possible.

The *conditioned frequency* of a combination was calculated from the product of the single frequencies of the predictors. The value was multiplied by 100 and the integer was taken. This results in the *number of patients in that combination* which is a proportional representation of that combination in the population.

The *conditioned probability of PONV* ($P_{(PONV)}$) for that combination was calculated by the sum of the coefficients according to the presence of the predictors and submitted to a logit transformation $P_{(PONV)}=1/(1+e^{-(\text{sum of coefficients})})$.

The number of patients with PONV was derived from the number of patients in that combination multiplied by the conditioned probability.

All *patients in that combination* were added (=total number of patients=population). All *patients with PONV* were added and divided by the total number of patients (=incidence of PONV). A constant was fitted into the calculation of the conditioned probability of PONV until the aimed incidence of PONV was reached (regression process).

References

1 Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000; **59**: 213–43

2 Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 46S–59S

3 Tramèr MR, Moore RA, Reynolds DJ, *et al.* A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. *BMJ* 1997; **314**: 1088–92

4 Sneyd JR, Carr A, Byrom WD, *et al.* A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. *Eur J Anaesthesiol* 1998; **15**: 433–45

5 Figueredo ED, Canosa LG. Prophylactic ondansetron for postoperstive emesis. Meta-analysis of its effectiveness in patients with previous history of postoperative nausea and vomiting. *Acta Anaesthesiol Scand* 1999; **43**: 637–44

6 Scuderi PE, James RL, Harris L, *et al.* Antiemetic prophylaxis does not improve outcomes after outpatient surgery when compared to symptomatic treatment. *Anesthesiology* 1999; **90**: 360–71

7 White PF, Watcha MF. Postoperative nausea and vomiting: prophylaxis versus treatment [editorial]. *Anesth Analg* 1999; **89**: 1337–9

8 Watcha MF. The cost-effective management of postoperative nausea and vomiting [editorial]. *Anesthesiology* 2000; **92**: 931–3

9 Palazzo M, Evans R. Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment. *Br J Anaesth* 1993; **70**: 135–40

10 Koivuranta M, Läärä E, Snare L, *et al.* A survey of postoperative nausea and vomiting. *Anaesthesia* 1997; **52**: 443–9

11 Apfel CC, Läärä E, Koivuranta M, *et al.* A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999; **91**: 693–700

12 Toner CC, Broomhead CJ, Littlejohn IH, *et al.* Prediction of postoperative nausea and vomiting using a logistic regression model. *Br J Anaesth* 1996; **76**: 347–51

13 Apfel CC, Greim CA, Haubitz I, *et al.* The discriminating power of a risk score for postoperative vomiting in adults undergoing various types of surgery. *Acta Anaesthesiol Scand* 1998; **42**: 502–9

14 Eberhart LH, Hogel J, Seeling W, *et al.* Evaluation of three risk scores to predict postoperative nausea and vomiting. *Acta Anaesthesiol Scand* 2000; **44**: 480–8

15 Sinclair D, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology* 1999; **91**: 109–18

16 Cohen MM, Duncan PG, DeBoer DP, *et al.* The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg* 1994; **78**: 7–16

17 Apfel CC, Greim CA, Haubitz I, *et al.* A risk score to predict the

probability of postoperative vomiting in adults. *Acta Anaesthesiol Scand* 1998; **42**: 495–501

18 Haigh CG, Kaplan LA, Durham JM, *et al.* Nausea and vomiting after gynaecological surgery: a meta-analysis of factors affecting their incidence. *Br J Anaesth* 1993; **71**: 517–22

19 Apfel CC, Palazzo M, Koivuranta M, *et al.* Models for predicting PONV are well established. Data acquisition and analysis bias of a new model may not add to current knowledge. *Anesthesiology* 2000; **92**: 1489–92

20 Hanley JA, McNeil BJ. The meaning and use of the area under a ROC curve. *Radiology* 1982; **143**: 29–36

21 Hanley JA, McNeil BJ. A method of comparing the area under receiver operating chacteristic curves derived from the same cases. *Radiology* 1983; **148**: 839–43

22 Matson A, Palazzo M. Postoperative nausea and vomiting. In: Adams AP and Cashman JN (eds). *Recent Advances in Anaesthesia and Analgesia*, Vol. 19. London: Churchill-Livingstone, 1995; 107–126

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Downward movement of syringe pumps reduces syringe output

H. Kern[1]*, A. Kuring[2], U. Redlich[1], U. R. Döpfmer[1], N. M. Sims[3], C. D. Spies[1] and W. J. Kox[1]

[1]Department of Anaesthesiology and Intensive Care Medicine, University Hospital Charite, Campus Mitte, Humboldt University of Berlin, Schumanstrasse 20/21, D-10117 Berlin, Germany. [2]Department of Biomedical Engineering, University of Jena, Germany. [3]Department of Anesthesia and Partners Healthcare Biomedical Engineering, Massachusetts General Hospital, Harvard Medical School, Boston, USA

**Corresponding author*

We studied how lowering a syringe pump and changing the outflow pressure could affect syringe pump output. We experimentally reduced the height of three different syringe pump systems by 80 cm (adult setting) or 130 cm (neonatal setting), as can happen clinically, using five flow rates. We measured the time of backward flow, no flow and the total time without flow. An exponential negative correlation was present between infusion rate and time without flow (r^2=0.809 to 0.972, P<0.01). Minimum flow rates of 4.4 and 2.6 ml h^{-1} respectively were calculated to give 60 and 120 s without infusion. The compliance of the different syringe pumps and their infusion systems was linearly correlated with the effective time without infusion (r^2=0.863, P<0.05). We conclude that the height of the syringe pumps should not be changed during transportation. If vertical movement of the syringe pump is necessary, the drugs should be diluted so that the flow rate is at least 5 ml h^{-1}.

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Anecdotal reports have noted changes in haemodynamics and oxygenation of neonates and older children due to flow-rate variability of dopamine or epinephrine infusions, in some cases requiring cardiopulmonary resuscitation.[1 2] Variation in flow rate affects nitroprusside pharmacodynamics in adults and children receiving continuous nitroprusside infusions.[3] Moving patients after surgery to the intensive care unit can destabilize them if they are being treated with catecholamines.[4] Lifting an infusion pump containing epinephrine by 80–100 cm while moving a patient from the operating table into bed after surgery led to critical increases in heart rate, blood pressure and left atrial pressure.[5] Experimentally, raising or lowering a syringe pump by 100 cm caused bolus administration or a critical delay in infusion, depending on the infusion rate. We found similar effects especially in newborns after correction of congenital heart disease. Lowering the syringe pump by a maximum of 80 cm in adults and by 130 cm in neonates could occur when preparing patients for transport from the theatre to the intensive care unit (Fig. 1). We set out to measure (i) the delay of different syringe pumps after lowering the height of the pump by the maximum distance found in clinical practice; (ii) the effect of infusion rate on the output of the syringe pump when the outflow pressure was altered by lowering the syringe pump; (iii) the minimum infusion rate for each syringe pump system that gave a predetermined delay of infusion.

Materials and methods

The infusion volume during the change in outflow pressure and the time without efficient infusion for the patient were measured in a closed system using glass capillaries of 0.5 mm diameter and a total length of 1 m. At the end of the capillaries, a manometer was used to simulate a central venous pressure of 8 mm Hg (Fig. 2).

One hour before changing outflow pressure, syringes were connected with the closed system and pumps were started with a minimum flow rate of 1 ml h^{-1}. They were kept running throughout the experiment. When a coloured fluid reached a marked area of the capillaries, the syringes were lowered by 80 or 130 cm for adult and neonatal settings respectively, and the time until the marked area was reached again was measured. The following values were determined: (i) the time of the reflux back into the infusion system of the liquid column; (ii) the distance of the reflux of

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the liquid column; (iii) the time without movement of the liquid column; and (iv) the time for the liquid column to reach the starting position again.

The infusion volume that was not administered was calculated according to the stopped time and flow rate (Fig. 3). This experiment was done using flow rates of 1, 2, 3, 5 and 10 ml h^{-1} and repeating each measurement eight to 10 times. Afterwards, the syringes and the infusion systems were connected to a commercially available transducer (Ohmeda, Murray Hill, NJ, USA) and a patient monitor (Solar 8000; Marquette Medical Systems, Milwaukee, WI, USA) to determine the compliance of the different systems. The pressure increase from 0 to 300 mm Hg was timed at 25 mmHg intervals and the compliance of the different systems was calculated according to $c=\Delta v/\Delta p$ using two flow rates.

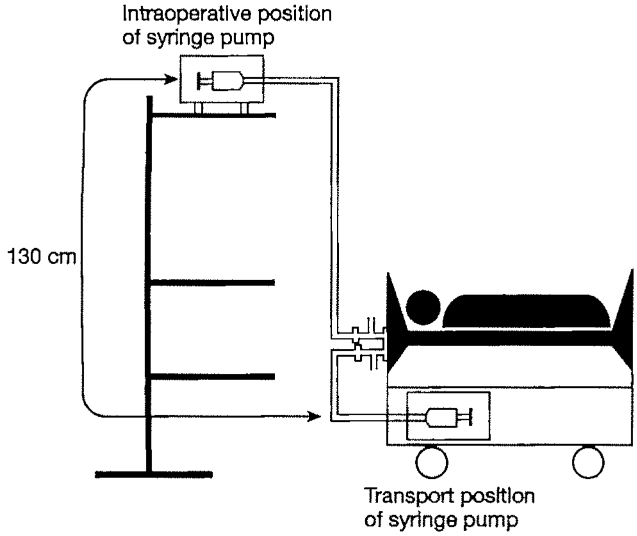
Intraoperative position of syringe pump
130 cm
Transport position of syringe pump

Fig 1 The drawing demonstrates the clinical practice of lowering the syringe pump from the position used during the operation to the bottom of the incubator for transport.

Materials

Three syringe pumps with their infusion systems were tested: (i) Injectomat-C (Frisenius, Oberursel, Germany) with a 150 cm infusion system (9000911); (ii) Ivac 770 (Ivac, San Diego, CA, USA) with a 200 cm infusion system (G30402); and (iii) Perfusor fm (B. Braun Melsungen Medical, Melsungen, Germany) with a 150 cm infusion system (N872 296/0).

A 50 ml Injectomat syringe was used for all experiments. The tested syringe pumps were used in clinical routine and were therefore checked regularly according to German law (Medizinproduktegesetz).

Statistical analysis

Results are given as mean (standard deviation) after normal distribution had been confirmed with the Kolmogorov–Smirnov test. The exponential correlation between pairs of variables was tested by r^2 and linear correlation was determined with the Pearson correlation coefficient. An exponential regression model was tested and the flow rate for a predetermined time without infusion was calculated for each system. The level of significance was $P<0.05$. We used the software package SPSS 8.0 (SPSS, Chicago, IL, USA).

Results

Changing the outflow pressure by lowering the syringe pump by 80 and 130 cm reduced the delivered infusion by between 633 and 23 s depending on the flow (Table 1).

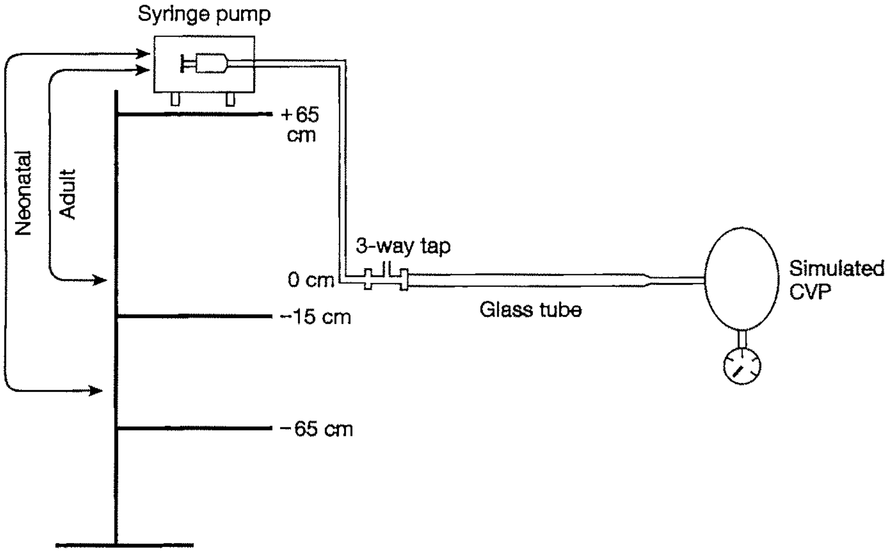

Fig 2 The experimental study simulating lowering the syringe pumps by 80 cm (adult setting) or 130 cm (neonatal setting). CVP, central venous pressure.

There was a statistically significant ($P<0.01$), exponentially negative correlation between flow rate and time without effective infusion for all three systems tested. Using this exponential regression, we estimated the flow rates when there would be an effective time without infusion of 60 and 120 s (Table 2). These rates were a minimum of 4.4 ml h^{-1} for 60 s without infusion and a minimum of 2.6 ml h^{-1} for 120 s without infusion for the adult setting. Lowering the syringe pump by 130 cm (neonatal setting), a minimum infusion rate of 6.0 ml h^{-1} gave a time of 60 s and 4.3 ml h^{-1} gave a time of 120 s without infusion. Testing the compliance of the different systems resulted in similar values for the Injectomat-C and the Perfusor fm (81 and 85 µl mm Hg^{-1} respectively). The compliance of the Ivac 770 system was greater, at 103 µl mm Hg^{-1}. There was a statistically significant positive correlation ($r^2=0.863$, $P<0.05$) between time without infusion and the compliance of the system.

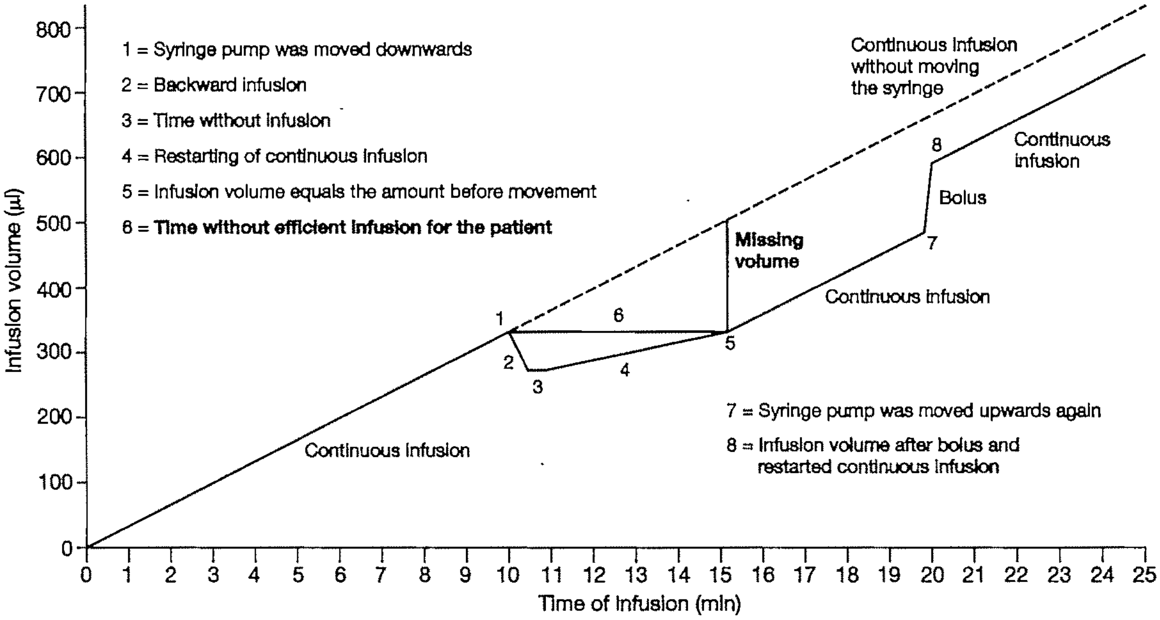
1 = Syringe pump was moved downwards
2 = Backward infusion
3 = Time without infusion
4 = Restarting of continuous infusion
5 = Infusion volume equals the amount before movement
6 = Time without efficient infusion for the patient
Continuous infusion without moving the syringe
Continuous infusion
Bolus
Missing volume
Continuous infusion
Continuous infusion
7 = Syringe pump was moved upwards again
8 = Infusion volume after bolus and restarted continuous infusion
Infusion volume (µl)
0
100
200
300
400
500
600
700
800
Time of infusion (min)
0
1
2
3
4
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Fig 3 Changes in infusion volume–time relationship during movement of the syringe pump. The drawing shows the experimental procedure and the measurement of time with no flow and the missing volume.

Table 1 Time without effective infusion after changing hydrostatic pressure using different flow rates. Results are shown as mean (standard deviation) after confirming normal distribution with the Kolmogorov–Smirnov test

Flow rate (ml h^{-1})	Adult setting		Neonatal setting	
	Time with no flow (s)	**Regression analysis**	**Time with no flow (s)**	**Regression analysis**
Injectomat-C				
1	234 (21)	$r^2=0.891$	417 (59)	$r^2=0.900$
2	129 (14)	$P\leq0.01$	260 (23)	$P\leq0.01$
3	81 (7)		156 (14)	
5	43 (3)		103 (6)	
10	23 (2)		45 (2)	
Ivac 770				
1	430 (27)	$r^2=0.972$	633 (65)	$r^2=0.931$
2	310 (24)	$P\leq0.01$	366 (18)	$P\leq0.01$
3	243 (10)		370 (13)	
5	130 (7)		212 (9)	
10	63 (2)		100 (2)	
Perfusor fm				
1	283 (18)	$r^2=0.809$	409 (14)	$r^2=0.849$
2	110 (9)	$P\leq0.01$	189 (10)	$P\leq0.01$
3	67 (5)		125 (7)	
5	39 (1)		109 (5)	
10	29 (1)		48 (1)	

Table 2 Flow rates for predicted times without infusion, calculated for each system according to a logistic linear regression model

Predicted time with no flow (s)	Flow rate (ml h^{-1})					
	Injectomat		Ivac		Perfusor	
	Adult	Neonatal	Adult	Neonatal	Adult	Neonatal
60	4.7	6.6	8.8	9.8	4.4	6.0
120	2.6	4.8	6.2	7.7	2.9	4.3

Discussion

We found that moving syringe pumps downwards, as we have been doing during transport after cardiac surgery, reduced the flow from the syringe pumps. The time without infusion was related to the infusion rate. Differences between the systems tested were probably caused by the different compliances of the connected infusion systems, and were correlated linearly with the observed time without infusion. The data presented do not endorse any particular manufacturer or model as an infusion device.

Variation in flow rate from syringe pumps has been shown in experimental and clinical settings.[2 3 6] Differences in relative syringe pump height during transport are frequent during paediatric cardiac surgery. When transport incubators are used the syringe pumps may be lowered suddenly. Changes in flow of vasoactive drugs may contribute to the haemodynamic instability often seen when moving intensive care patients.[7] Relevant time without infusion was found up to infusion rates of >5 ml h^{-1}. The greater compliance of the Ivac 770 system influenced the marked effect of changes in outflow pressure on this apparatus. The greater length of the system (200 cm compared with 150 cm for the Injectomat-C and Perfusor fm) and the specific pressure transducer membrane could cause an enlarged filling volume, despite the favourably low relative piston compliance.[8] Because we wished to simulate clinical conditions, we did not change the infusion systems and we compared the Ivac 770 system as it is used clinically.

Variation in drug delivery at different flow rates was simulated in previous studies using a computerized gravimetric technique.[9] We wanted to go further and demonstrate the individual flow rates using a fixed pressure of 8 mm Hg working against the infusion, comparable to the central venous pressure in a clinical setting. With this technique we could show the time of retrograde flow, the time with no flow and the time taken to return to the original infusion volume (i.e. the volume before the syringe pump's position was changed). A clinical study was not appropriate for ethical reasons, because a direct relationship between haemodynamic response and drug administration is known.[3]

In conclusion, the height of a syringe pump, used to give vasoactive agents, relative to the patient should not be changed for transport. If a change in the syringe pump's position is inevitable, the concentration of the drugs administered should be adjusted so that flow rates of at least 5 ml h^{-1} are required. Infusion systems with a small filling volume and small compliance are advantageous.

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References

1 Schulze KF, Graff M, Schimmel MS, *et al.* Physiologic oscillations produced by an infusion pump. *J Pediatr* 1983; **103**: 796–8
2 Klem SA, Farrington JM, Leff RD. Influence of infusion pump operation and flow rate on hemodynamic stability during epinephrine infusion. *Crit Care Med* 1993; **21**: 1213–7
3 Hurlbut JC, Thompson S, Reed MD, *et al.* Influence of infusion pumps on the pharmacologic response to nitroprusside. *Crit Care Med* 1991; **19**: 98–101
4 Russel GB, Myers JL, Kofke WA. The first 24 h postoperatively. In: Hensley FA, Martin DE, eds. *The Practice of Cardiac Anesthesia.* Boston: Little, Brown, 1990; 289–301
5 Krauskopf KH, Rauscher J, Brandt L. Influence of hydrostatic pressure on continuous application of cardiovascular drugs with syringe pumps. *Anaesthesist* 1996; **45**: 449–52
6 Stull JC, Erenberg A, Leff RD. Flow rate variability from electronic infusion devices. *Crit Care Med* 1988; **16**: 888–91
7 Evans A, Winslow EH. Oxygen saturation and hemodynamic response in critically ill, mechanically ventilated adults during intrahospital transport. *Am J Crit Care* 1995; **4**: 106–11
8 Crisp CB, Slate J, Lovy D. Infusion pump operation, flow rate, and hemodynamic stability during epinephrine infusion. *Crit Care Med* 1994; **22**: 1339–40
9 Leff RD, True WR, Roberts RJ. A gravimetric technique for evaluating flow continuity from two infusion devices. *Am J Hosp Pharm* 1987; **44**: 1388–91

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LABORATORY INVESTIGATIONS

Influence of sepsis on sevoflurane minimum alveolar concentration in a porcine model†

B. Allaouchiche[1]*, F. Duflo[1], J.-P. Tournadre[1], R. Debon[1] and D. Chassard[2]

[1]*Department of Anaesthesiology and Intensive Care, Hotel-Dieu Hospital, Lyon, France.* [2]*Department of Research 18/96, Claude Bernard University, Lyon, France*

**Corresponding author: Anaesthesiology and Intensive Care Department, Hotel-Dieu Hospital, 1 place de l'hôpital, F-69288 Lyon cedex 02, France*

Sevoflurane is widely used in anaesthetic protocols for patients undergoing surgical procedures. However, there are no reports on the influence of sepsis on minimum alveolar concentration of sevoflurane (MAC_{SEV}) in animals or in humans. The aim of this study was to test the hypothesis that sepsis could alter the MAC_{SEV} in a normotensive septic pig model. Twenty young, healthy pigs were used. After they had received 10 mg kg^{-1} of ketamine i.m. for premedication, anaesthesia was established with propofol 3 mg kg^{-1} and the trachea was intubated. Sevoflurane was used as the sole anaesthetic agent. Baseline haemodynamic recording included electrocardiography, carotid artery blood pressure and a pulmonary thermodilution catheter. Baseline MAC_{SEV} in each pig was evaluated by pinching with a haemostat applied for 1 min to a rear dewclaw. MAC_{SEV} was determined using incremental changes in sevoflurane concentration until purposeful movement appeared. Pigs were assigned randomly to two groups: the saline group (n=10) received a 1-h i.v. infusion of sterile saline solution while the sepsis group (n=10) received a 1-h i.v. infusion of live *Pseudomonas aeruginosa*. Epinephrine and hydroxyethylstarch were used to maintain normotensive and normovolemic haemodynamic status. In both groups, MAC_{SEV} was evaluated 5 h after infusion. Significant increases in mean artery pulmonary pressure, filling, epinephrine and vascular pulmonary resistances occurred in the sepsis group. MAC_{SEV} for the saline group was 2.4% [95% confidence interval (CI) 2.1–2.55%] and the MAC_{SEV} for the sepsis group was 1.35% (95% CI 1.2–1.45%, $P<0.05$). These data indicate that MAC_{SEV} is significantly decreased in this normotensive septic pig model.

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Patients with sepsis syndrome or septic shock may require general anaesthesia for eradication of a septic focus, often on an emergency basis. Most anaesthetics are cardiodepressant and can alter vascular tone. Nevertheless, ketamine preserves cardiovascular function and oxygen delivery in hypoxic tissues and therefore seems to be the most attractive drug in these circumstances.[1] Theoretically, sevoflurane could be an interesting alternative in these patients because of its rapid pharmacokinetics, allowing rapid haemodynamic control.[2]

The pharmacokinetics of sevoflurane has been well characterized in animals and humans in numerous situations.[3] As with other inhaled anaesthetic agents, many parameters can affect the minimum alveolar concentration of sevofluorane (MAC_{SEV}) in pigs, including age, hypothermia, additional anaesthetic drugs, acid–base status, carbon dioxide and cerebral electrolyte concentrations, type of supramaximal stimulus and haemodynamics.[4–7] Reduced requirement of isoflurane MAC has been demonstrated in a septic canine model,[8] but no published data are available on MAC_{SEV} requirements in septic animals or patients.

As few studies have evaluated the use of halogenated agents in septic conditions, inappropriately high or low

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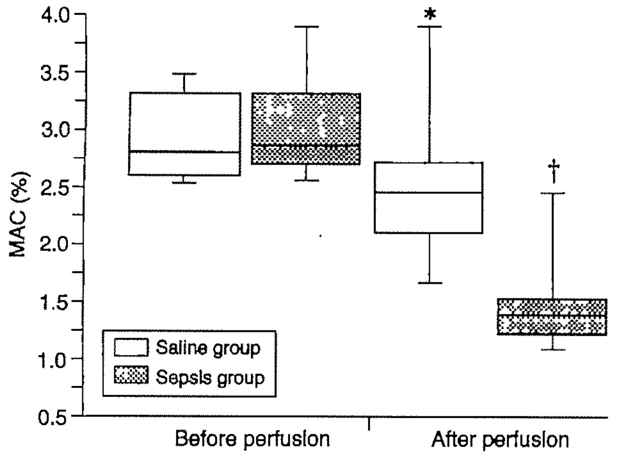

Fig 1 MAC$_{\text{SEV}}$ (%) before (control) and after infusion (saline and sepsis), shown as median and 95% confidence interval. *P not significant *vs* control after saline infusion; †$P<0.05$ *vs* control after bacterial infusion.

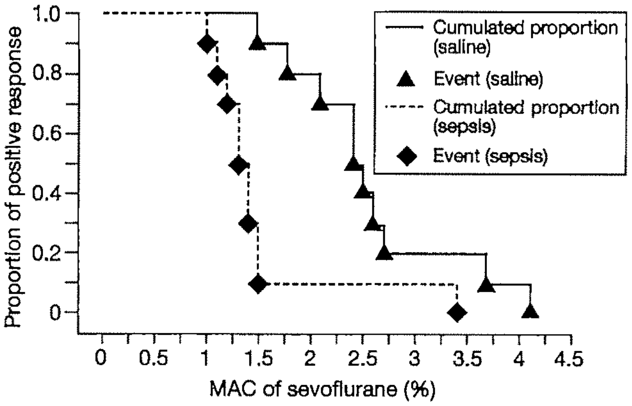

Fig 2 Kaplan–Meier curve of movement fitted for MAC$_{\text{SEV}}$ with (bacterial infusion) and without (saline infusion) sepsis. In these dose–response curves the percentage of animals that showed a response is plotted against the sevoflurane concentration.

doses of volatile agents may have been administered. The aim of this study was to test whether sepsis could modify MAC$_{\text{SEV}}$ requirements in an animal model of sepsis.

Methods

After approval of the study by the Claude Bernard University Committee on Animal Research, we studied 20 healthy young pigs [3–4 months old; 23 (SD 2) kg]. They were obtained from Morel Farm and housed in the university vivarium for 3–5 days.

After premedication with ketamine 10 mg kg^{-1} i.m., general anaesthesia was induced with propofol 3 mg kg^{-1} infused in an auricular vein. The trachea was intubated with a 6.0 mm cuffed tube and mechanical ventilation was started. Ventilation was performed (Sa 2; Dräger, Lübeck, Germany) in a pure oxygen non-rebreathing system with sevoflurane as the sole anaesthetic agent, delivered with a calibrated vaporizer (Vapor 19.1; Dräger). Fresh gas flow was delivered at 4.5 litre min^{-1} in this open circuit, and ventilation was adjusted to maintain end-tidal normocapnia at baseline values. A 7 Fr pulmonary artery thermodilution catheter (Arrow, PA, USA) was introduced via the internal jugular vein, positioned under fluoroscopy into the pulmonary artery for measurement of pulmonary arterial pressure (MPAP) and cardiac output. A common carotid artery catheter was inserted for continuous monitoring of systemic arterial pressure and blood sampling. Inspired and expired gases, including end-tidal anaesthetic concentrations and carbon dioxide concentrations, were measured with a recently calibrated gas analyser (Dräger). Sevoflurane was measured with an infrared analyser (PM 8050; Dräger). This analyser was calibrated before the study according to the manufacturer's guidelines with specific software using anaesthetic gas mixtures of known concentration: oxygen, carbon dioxide, nitric oxide and halogenated volatiles. During the whole procedure, hydration was maintained with a 9‰ solution of NaCl 5 ml^{-1} kg^{-1} h^{-1} as the sole perfusate.

MAC$_{\text{SEV}}$ was then assessed in each pig as previously described,[5 6] beginning with a 3.5% end-tidal concentration of sevoflurane, according to previous studies.[2 7] Each pig was pinched with a haemostat clamped with full ratchet lock to the back limb and moved cranially and caudally for 1 min. If no response was obtained, the expired concentration of sevoflurane was decreased by 0.1% over 10 min for equilibration ($F_A/F_I=1$) and MAC$_{\text{SEV}}$ was evaluated. Once MAC$_{\text{SEV}}$ had been determined, the following data were recorded: heart rate, systemic arterial pressure, MPAP, central venous pressure, end-tidal carbon dioxide, central core temperature, filling levels, cardiac output. An arterial blood sample was collected simultaneously for immediate gas analysis on an automated blood gas analyser (ABL5; Radiometer, Neuilly, France). Another arterial blood sample was collected and centrifuged (E82S; Jouan, Lyon, France) for measurements of plasma lactate levels.

Once the MAC$_{\text{SEV}}$ had been determined and haemodynamic data collected, pigs were allocated randomly to two groups. The saline group received a 1-h infusion of sterile saline solution (1 ml kg^{-1}) and the sepsis group a 1-h intravenous infusion of live *Pseudomonas aeruginosa*. This pure strain was isolated from an abscess and remained unchanged during the entire study. The inoculum was evaluated with a turbidity analyser: 1.5 McFarland units corresponding to 5×10^8 colony-forming units (c.f.u.) per ml. In keeping with previous studies, 0.3 ml 20 kg^{-1} min^{-1} of 5×10^8 c.f.u. per ml live bacteria was infused.[9 10]

In both groups, haemodynamic status and core temperature were assessed 30, 60, 120, 180, 240 and 300 min after bacterial or saline infusion. Epinephrine and hydroxyethylstarch were used to maintain a pulmonary artery occlusion pressure between 8 and 15 mm Hg and a mean arterial

Table 1 Influence of sepsis on sevoflurane MAC. Data are mean (SEM). MPAP=mean pulmonary artery pressure; PAOP=pulmonary arterial occlusion pressure; cumulative filling=hydroxyethylstarch and saline infusion. $^*P<0.05$ *vs* animals with saline

		Time after infusion (min)					
	Before infusion	**30**	**60**	**120**	**180**	**240**	**300**
Systemic vascular resistance (dyne s cm^{-5})							
Saline	1918 (140)	2208 (156)	2134 (144)	1987 (144)	2170 (152)	2079 (210)	2165 (176)
Sepsis	2025 (110)	1735 (89)	1825 (101)	1944 (78)	1972 (134)	2085 (128)	2061 (193)
PAOP (mm Hg)							
Saline	11 (0.2)	10 (0.3)	12 (0.5)	11 (0.3)	9 (0.1)	11 (0.2)	13 (0.5)
Sepsis	12 (0.5)	11 (0.3)	10 (0.3)	8 (0.2)	10 (0.3)	12 (0.4)	11 (0.6)
MPAP (mm Hg)							
Saline	16.4 (1.2)	18 (1.5)	14.7 (1.4)	16.1 (1.2)	15.7 (1.4)	14.5 (1.4)	14.6 (1.3)
Sepsis	19.5 (1.8)	45 (3.4)*	43.2 (1.5)*	38.9 (1.6)*	36.5 (1.1)*	37.1 (1.7)*	34.2 (1.8)*
Pulmonary vascular resistance (dyne s cm^{-5})							
Saline	211 (26)	198 (41)	179 (21)	214 (29)	202 (19)	230 (28)	189 (32)
Sepsis	242 (38)	722 (102)*	690 (64)*	654 (45)*	589 (31)*	603 (63)*	554 (100)*
Heart rate (beats min^{-1})							
Saline	89 (5)	95 (4)	87 (7)	92 (4)	111 (9)	98 (3)	105 (2)
Sepsis	101 (6)	104 (6)	94 (4)	106 (9)	88 (5)	84 (10)	90 (9)
MAP (mm Hg)							
Saline	78 (12)	79 (16)	77 (11)	70 (9)	71 (10)	81 (13)	80 (14)
Sepsis	85 (15)	61 (9)	69 (8)	71 (14)	77 (31)	93 (17)	86 (11)
Cardiac output (litre min^{-1})							
Saline	2.8 (0.3)	2.5 (0.4)	2.4 (0.3)	2.4 (0.5)	2.2 (0.6)	2.7 (0.2)	2.5 (0.2)
Sepsis	2.9 (0.3)	2.3 (0.7)	2.5 (0.6)	2.6 (0.4)	2.7 (0.8)	3.1 (0.3)	2.9 (0.5)
Core temperature (°C)							
Saline	38 (0.2)	38.2 (0.3)	38.2 (0.4)	38.4 (0.2)	38.1 (0.4)	38.8 (0.7)	38.6 (0.6)
Sepsis	38.1 (0.2)	38.3 (0.3)	38.3 (0.2)	38.4 (0.5)	38.6 (0.5)	38.3 (0.4)	38.7 (0.6)
Plasma lactate concentration (mmol litre^{-1})							
Saline	1.1 (0.2)	–	–	–	–	–	1.4 (0.3)
Sepsis	0.9 (0.3)	–	–	–	–	–	1.5 (0.6)
Epinephrine (µg kg^{-1} min^{-1})							
Saline	0	0	0	0	0	0	0
Sepsis	0	1.1 (0.2)*	0.9 (0.3)*	0.8 (0.2)*	0.6 (0.2)*	0.7 (0.3)*	0.6 (0.3)*
Cumulative filling (ml)							
Saline	30 (0)	60 (0)	90 (0)	120 (0)	150 (0)	180 (0)	210 (0)
Sepsis	30 (0	114 (16)*	197 (23)*	264 (27)*	367 (39)*	398 (33)*	454 (42)*

pressure (MAP) between 60 and 70 mmHg.[11] MAC$_{SEV}$ was assessed again 5 h after the end of the infusion.

MAC$_{SEV}$ data were compared using the Mann–Whitney *U*-test (Fig. 1) and Kaplan–Meier curve analysis (Fig. 2). Dose–response curves were constructed in which the percentage of animals that had a demonstrated response was plotted against the sevoflurane concentration. Median MAC$_{SEV}$ and the 95% confidence intervals were calculated. The haemodynamic data were compared using the Friedman test (Table 1). When differences were observed, a pairwise comparison using the Student–Newman–Keuls test was performed to determine which groups differed. Results are presented as mean (SEM) in Table 1 and as percentages of values for the control group. MAC$_{SEV}$ is expressed as median and 95% confidence interval.

Results

Significant differences in MAC$_{SEV}$ were found between the sepsis and saline groups: MAC$_{SEV}$ for the saline group was 2.4% (2.1–2.55%) and the MAC$_{SEV}$ for the sepsis group was 1.35% (1.2–1.45%) ($P<0.05$) (Figs 1 and 2).

Mean MPAP in the sepsis group had increased significantly (+131%, $P<0.05$) 30 min after the end of the bacterial perfusion. It then decreased continuously to a steady state with persistent pulmonary hypertension for the remainder of the study in comparison with the control group (+78%) (Table 1). Pulmonary vascular resistance had increased significantly (+179%; $P<0.05$) in the sepsis group 30 min after the end of the bacterial perfusion; it then declined but remained significantly higher compared with baseline (+114%, $P<0.05$) (Table 1). Filling level increased significantly in the sepsis group during the entire study after the end of bacterial infusion (+300%, $P<0.05$) (Table 1). Epinephrine infusion increased significantly in the sepsis group during the whole study after the end of bacterial infusion (Table 1).

In both groups, before and after infusion, no statistically significant differences were observed for MAP, cardiac output, systemic vascular resistance, heart rate, central venous pressure, pulmonary artery occlusion pressure, filling, end-tidal carbon dioxide, arterial gas values, core temperature or plasma lactate concentration (Table 1).

No statistically significant differences were observed for all parameters and MAC_{SEV} in the saline group when values before and after perfusion of sterile saline were compared (Table 1) (Figs 1 and 2).

Discussion

In comparison with the non-septic group (saline group), septic animals had a decreased inhalation requirement for sevoflurane, corresponding to a lower MAC_{SEV}.

The experimental model used has several limitations. First, of the numerous models of experimental sepsis found in the literature, only a few have been described to assess MAC of volatile or intravenous anaesthetic needs or haemodynamic effects.[8] [12] Intravasal or intraperitoneal injection of live microorganisms or purified endotoxin and many methods of caecal ligation have been used, but no ideal model of sepsis is available. Injection of a defined amount of microorganisms can provide simple and satisfactory standardization of the inoculum and consequently a highly reproducible sepsis model.[13] However, this approach has at least two disadvantages. The virulence can vary from one bacterial strain to another and intravenous bolus injection of live microorganisms does not resemble any situation in clinical medicine.[13] Accordingly, in our study we used continuous intravenous perfusion of *P. aeruginosa* from a constant pure strain.

Secondly, the haemodynamic values in our study had a particular profile. Because of epinephrine and filling, no significant differences were found for MAP, cardiac output, systemic vascular resistance, CVP and pulmonary artery occlusion pressure in the septic group (Table 1). Moreover, heart rate did not increase significantly in the septic pig group because of the negative lusitropic effect of sevoflurane (Table 1).[2] Finally, because of the microorganism infusion, early pulmonary hypertension appeared[9] and a slight decrease in MPAP was observed over the whole period of the study, even after bacterial perfusion. Overall, we obtained a normotensive resuscitated septic pig model with normal systemic resistances and cardiac output, close to that found in patients undergoing surgical procedures. Thirdly, because of the short delay after bacterial infusion, septic myocardiopathy probably did not occur. In cases of haemodynamic failure, MAC_{SEV} is likely to be altered more profoundly.

Three basic variables can influence the MAC: the nociceptive stimulus, the response and the end-tidal anaesthetic concentrations.[14] Two types of stimulus have been used to assess the MAC in animals: clamping the dewclaw and clamping the tail.[6] Minimum alveolar concentration values obtained by clamping the tail were more variable and lower than those obtained by clamping the dewclaw. Therefore, the stimulus that was applied in our study was dewclaw clamping, which has been reported to be a supramaximal stimulus.[6] This stimulus remained constant during the entire study. Thus, the nature of the stimulus could not influence MAC_{SEV}. The response to this supramaximal stimulus has already been described in the pig model as the 'pedal reflex'.[15] It is obtained when contralateral clamping is performed. This type of response was used in our study in order not to underestimate MAC_{SEV}.

Many pathophysiological conditions can affect MAC_{SEV} values, including additional anaesthetic drugs, differences in core temperature, age, acid–base status, cerebral electrolyte concentrations, hypotension and prolonged anaesthesia.[4] [7] [16] [17] MAC_{SEV} values in the control group were close to values reported by Eger.[4] The MAC_{SEV} reduction in the septic group could not be explained by core temperature modification. Values under 36°C define hypothermia in pigs.[18] Therefore, both groups were normothermic. In addition, there were no statistical differences between core temperature values in the two groups (Table 1).

Suspected occult tissue hypoxia associated with sepsis, producing metabolic acidosis and indicating anaerobic metabolism, probably contributed to the decreased anaesthetic requirement.[8] In our study, there was no difference in arterial lactate concentrations or acid–basis status. However, lactate is an unreliable indicator of tissue hypoxia during sepsis[19] and in our septic model, because of the short delay after bacterial infusion, tissue hypoxia could have occurred without metabolic modifications.

Another potential cause of discrepancy in the reduction of MAC_{SEV} is fluid and drug resuscitation. Hydroxyethylstarch and epinephrine were administered according to the anaesthetist's normal practice in order to sustain blood pressure. Steffey and Eger investigated the effect of various vasopressors on halothane MAC in normal dogs and found no effect of epinephrine.[20] Our results support the hypothesis that changes in anaesthetic requirement might be related, in part, to the use of hydroxyethylstarch. However, the influence of hydroxyethylstarch on MAC requirements has never been explored.

Differences in MAC_{SEV} could result from variation in the duration of the experimental procedure. This was not the case in this study as the duration of experiments was constant throughout the study.

Hypotension has been reported to decrease the MAC of volatile anaesthetic agents.[7] In our study, because of epinephrine and filling, septic pigs remained normotensive and had normal systemic vascular resistances.

Differences in MAC_{SEV} can also result from central nervous system dysfunction associated with sepsis. Encephalopathy, alterations in neurotransmitter levels, changes in receptor function and brain Ca^{2+} accumulation occur early during sepsis.[1] Furthermore, changes in regional blood flow and skeletal muscle energy status appear during sepsis.[21] Thus, anaesthetic requirements could be reduced in these models and could possibly explain the lower MAC_{SEV} in the septic group.

In summary, surgical procedures can be performed in patients with sepsis. Improvement in early diagnosis and fluid resuscitation has changed septic shock into severe normotensive sepsis. In this normotensive pig model, the MAC of sevoflurane is decreased. Further studies are needed to determine the effect of hepatic and renal alterations on sevoflurane metabolism in septic patients.

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References

1 Baxter F. Septic shock. *Can J Anaesth* 1997; **44**: 59–72

2 Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anaesthesia without and with 50% nitrous oxide. *J Pharmacol Exp Ther* 1984; **231**: 640–8

3 Yasuda N, Targ AG, Eger EI II, Johnson BH, Weiskopf RB. Pharmacokinetics of desflurane, sevoflurane, isoflurane, and halothane in pigs. *Anesth Analg* 1990; **71**: 340–8

4 Eger EI II. Desflurane animal and human pharmacology: aspects of kinetics, safety, and MAC. *Anesth Analg* 1992; **75**: S3–9

5 Moon PF, Scarlett JM, Ludders JW, Conway TA, Lamb SV. Effect of fentanyl on minimum alveolar concentration of isoflurane in swine. *Anesthesiology* 1995; **83**: 535–42

6 Eger EI II, Johnson BH, Weiskopf RB, Holmes MA, Yasuda N, Targ A, Rampil IJ. Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesth Analg* 1988; **67**: 1174–6

7 Vivien B, Langeron O, Coriat P, Riou B. Minimum alveolar anesthetic concentration of volatile anesthetics in normal and cardiomyopathic hamsters *Anesth Analg* 1999; **88**: 489–93

8 Gill R, Martin C, McKinnon T, Lam C, Cunningham D, Sibbald WJ. Sepsis reduces isoflurane MAC in a normotensive animal model of sepsis. *Can J Anaesth* 1995; **42**: 631–5

9 Bloomfield GL, Sweeney LB, Fisher BJ, *et al.* Delayed administration of inhaled nitric oxide preserves alveolar-capillary membrane integrity in porcine Gram-negative sepsis. *Arch Surg* 1997; **132**: 65–75

10 Ridings PC, Bloomfield GL, Holloway S, *et al.* Sepsis-induced acute lung injury is attenuated by selectin blockade following the onset of sepsis. *Arch Surg* 1995; **130**: 1199–208

11 Walsh CJ, Surgerman HJ, Mullen PG, et *al.* Monoclonal antibody to tumor necrosis factor α attenuates cardiopulmonary dysfunction in porcine Gram-negative sepsis. *Arch Surg* 1992; **127**: 138–45

12 Van der Linden P, Gilbart E, Engelman E, Schmartz D, de Rood M, Vincent JL. Comparison of halothane, isoflurane, alfentanil and ketamine in experimental septic shock. *Anesth Analg* 1990; **70**: 608–17

13 Giercksky KE, Lundblad R. Animal models of intra-abdominal sepsis. In: Jeppsson B, ed. *Animal Modelling in Surgical Research.* Amsterdam: Harwood Academic Publishers, 1998; 143–54

14 Eger EI II, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965; **26**: 756–63

15 Lundeen G, Manohar M, Parks C. Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anaesthesia with or without 50% nitrous oxide. *Anesth Analg* 1983; **62**: 499–512

16 Eger EI II. Uptake and distribution. In: Miller RD, ed. *Anaesthesia.* New York: Churchill Livingstone, 1994; 101–23

17 Tanifuji Y, Eger EI II. Brain sodium, potassium, and osmolality: effects on anesthetic requirement. *Anesth Analg* 1978; **57**: 404–10

18 Fritz H, Bauer R, Walter B, *et al.* Hypothermia related changes in electrocortical activity at stepwise increase of intracranial pressure in piglets. *Exp Toxicol Pathol* 1999; **51**: 163–71

19 James JH, Luchette FA, McCarter FD, Fisher JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet* 1999; **354**: 505–8

20 Steffey EP, Eger EI II. The effect of seven vasopressors on halothane minimum alveolar concentration in dogs. *Br J Anaesth* 1975; **47**: 435–8

21 Illner HP, Shires T. Membrane defect and energy status in rabbit skeletal muscle cells in sepsis and septic shock. *Arch Surg* 1981; **116**: 302–5

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Halothane potentiates the effect of methamphetamine and nomifensine on extracellular dopamine levels in rat striatum: a microdialysis study

Y. U. Adachi[1,2], K. Watanabe[1], T. Satoh[1] and E. S. Vizi[2]*

[1]*Department of Anesthesiology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan.* [2]*Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, PO Box 67, H-1450 Budapest, Hungary*

**Corresponding author*

Brain microdialysis was used to study the *in vivo* release and metabolism of dopamine (DA) in the rat striatum during halothane anaesthesia. Concentrations were measured in microdialysates collected every 20 min and applied directly to an on-line high-performance liquid chromatograph. Halothane was administered at concentrations of 0.5, 1.0, 1.5 and 2.0%. In another series of experiments, rats were treated intraperitoneally or locally with methamphetamine, a drug of abuse, or with nomifensine, a dopamine uptake blocker and antidepressant, in combination with 0.5 or 1.5% halothane. Halothane anaesthesia did not affect the dialysate (extracellular) concentration of DA at 2.0%. By contrast, the concentrations of DA metabolites [3-methoxytyramine (3-MT), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] increased during inhaled halothane anaesthesia in a dose-dependent manner and recovered after anaesthesia. Halothane potentiated the ability of methamphetamine to increase the extracellular concentration of DA when administered systemically, whereas only a small increase in DA accumulation was seen when methamphetamine was administered locally via the perfusate. Similarly, the increase in extracellular DA was accentuated by systemic nomifensine during halothane anaesthesia, but no obvious enhancement was observed when it was applied locally. It has been shown that the neurotoxic effect of methamphetamine is mediated by the suboxidation of DA released from the cytoplasm into the extracellular space and transformed into highly reactive free radicals. On the basis of our results, it is suggested that care should be exercised when halothane anaesthesia is used in patients abusing phenylethylamines (amphetamines) or being treated with DA uptake blockers (nomifensine).

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It has been shown[1] that the volatile anaesthetic isoflurane potentiates the ability of nomifensine to increase the extracellular dopamine (DA) concentration in the brain, probably by releasing DA from axon terminals. In addition, halothane has been reported to either increase[2–4] or not affect[5] the extracellular concentration of DA in the brain during anaesthesia. Miyano *et al.*[4] investigated the dose-dependency of the effect of halothane on the extracellular DA concentration, and concluded that the hypoxia induced by halothane may be responsible for the increased extracellular concentration of DA.[4 5] In addition, Fink-Jensen *et al.*[5] reported that halothane enhanced the ability of both nomifensine and vanoxerine (selective inhibitors of DA reuptake) to increase DA concentration. Moreover, Opacka-Juffry *et al.*[1] concluded that volatile anaesthetics modulate extracellular DA concentrations by acting on the dopaminergic axon terminals of the nigrostriatal pathway. However, until now no attempt has been made to reinvestigate the effect of halothane anaesthesia on extracellular concentrations of DA and its metabolites. Specifically, no previous studies have included comparison of systemically and locally administered methamphetamine and a DA reuptake inhibitor (nomifensine). These data may yield information regarding the site and mode of action of

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halothane. It is known that methamphetamine, a widely abused psychostimulant, releases DA from the cytoplasm of the axon terminals in the striatum,[6] [7] and nomifensine, a drug used world-wide for depression, prevents DA from being taken up. Therefore, the effect of halothane anaesthesia on the extracellular concentrations of DA and its metabolites [3-methoxytyramine (3-MT), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] was studied in the presence of methamphetamine or nomifensine.

Methods

The experiments were approved by the Committee for Animal Research of our college. Male Sprague–Dawley rats (SLC Laboratory, Tokyo, Japan), weighing 280–320 g, were used. The animals were kept at 20–22°C on a 12 h light–12 h dark cycle (lights on from 07:00 to 19:00 h). All animals had free access to food and drinking water.

Microdialysis

Rats were anaesthetized with sevoflurane and ventilated through an orotracheal tube. Surgical procedures were performed after topical application of 1% lidocaine. Using a stereotaxic apparatus, a unilateral guide cannula was implanted just above the striatum (AP +0.6 mm, ML +3.0 mm, DV −3.8 mm) according to the atlas of Paxinos and Watson.[8] The rats were allowed to recover for at least 2 days before experimentation. After each experiment, rats were killed by inhalation of excess isoflurane and intravenous injection of thiopental. Microdialysis probe placement was confirmed by histological examination.

Microdialysis probes were obtained from Eicom (Kyoto Japan) (outside diameter 0.22 mm, membrane length 3 mm, polycarbonate tubing, cut-off molecular weight 50 000). On the day of experimentation, at about 07:00 h, the rats were anaesthetized briefly with sevoflurane. The probe was inserted carefully into the striatum through a guide cannula and fixed to the cannula with a screw. This procedure was performed within 5 min of anaesthesia, after which the rat was placed immediately in a clear open Plexiglas box (15 litres in capacity, 27 cm in diameter and 26 cm in height) for recovery. Rats regained consciousness within approximately 3 min. After recovery, the probe was perfused continuously with Ringer solution[2–5] (in mEq litre^{-1}: 147.0 Na$^+$, 4.0 K$^+$, 2.4 Ca^{2+}, 155.8 Cl$^-$) at a flow rate of 2 μl min^{-1} using a microinfusion pump (ESP-64; Eicom) to determine baseline concentrations of DA and its metabolites. Samples were collected every 20 min and injected directly into an on-line analytical system with the autoinjector (EAS-20; Eicom) as described previously.[9–10] The concentrations of DA, DOPAC, 3-MT and HVA in each dialysate sample (40 μl/20 min) were determined by HPLC with an electrochemical detector (ECD-300; Eicom). These compounds were separated by reverse-phase ion-pair chromatography with a 5 μm C-18 column (MA5-ODS, 150×2.1 mm; Eicom) using isocratic mobile phase (0.1 M sodium acetate, 0.1 M citric acid, 1.4 mM sodium 1-octanesulphonate, 5 μM EDTA-Na$_2$ and methanol 13–14%, pH 3.9), delivered at a flow rate of 230 μl min^{-1} by a high-pressure pump (EP-300; Eicom). A guard column (MA, 5×4 mm; Eicom) prevented deterioration and plugging of the analytical column. The compounds were quantified by electrochemical detection using a glassy carbon working electrode set at 650 mV against an Ag/AgCl reference electrode. The detection limit for each of the compounds was about 0.1 pg per sample.

DA and its metabolites reached stable baseline concentrations about 4.5 h after microdialysis probe implantation. Thus, at least six dialysate samples (each 40 μl collected in 20 min) were collected before starting an experiment. The mean value obtained from the last three samples was used as baseline release. The time when a pharmacological manipulation started will be hereafter termed ‘Fr. 1’ (fraction 1).

Experiment 1

Each rat was anaesthetized in the semi-closed Plexiglas box, into which 3% halothane was initially introduced at a rate of 3 litre min^{-1} for about 5 min until a steady state was achieved; subsequently 0.5, 1.0, 1.5 or 2.0% halothane was applied at rate of 2 litre min^{-1}, using air (23% oxygen) as a carrier. The control group was administered air through the same line and at the same rate. After a steady state had been achieved, each concentration of halothane was administered for 1 h from Fr. 1 while striatal dialysates were collected. The anaesthetic gas was introduced to the centre of the box and escaped through several small holes used for connecting the rat to the analytical apparatus. Dialysate sampling was continued for 4 h after the conclusion of 1 h of anaesthesia. The rectal temperature of the rat was monitored and maintained at 37°C with an electrical heating pad, except in the control and 0.5% halothane groups, because the animals were consistently awake during inhalation. The concentrations of volatile gas and oxygen in the box were monitored with the infrared anaesthetic gas analyser (Capnomac Ultima; Datex, Helsinki, Finland) during each anaesthetic. Immediately after 1 h of anaesthesia, the gas in the box was exchanged for room air by forced ventilation.

Experiment 2

Methamphetamine and nomifensine maleate were tested systemically. Methamphetamine and nomifensine were dissolved in physiological saline (with warming for nomifensine), achieving final concentrations of 5 and 1 mg ml^{-1} respectively. At Fr. 1, either methamphetamine 2 mg kg^{-1} (0.6 ml/300 g) or nomifensine 10 mg kg^{-1} (0.6 ml/300 g) was injected intraperitoneally, with or without subsequent inhalation of 0.5 or 1.5% halothane for 1 h.

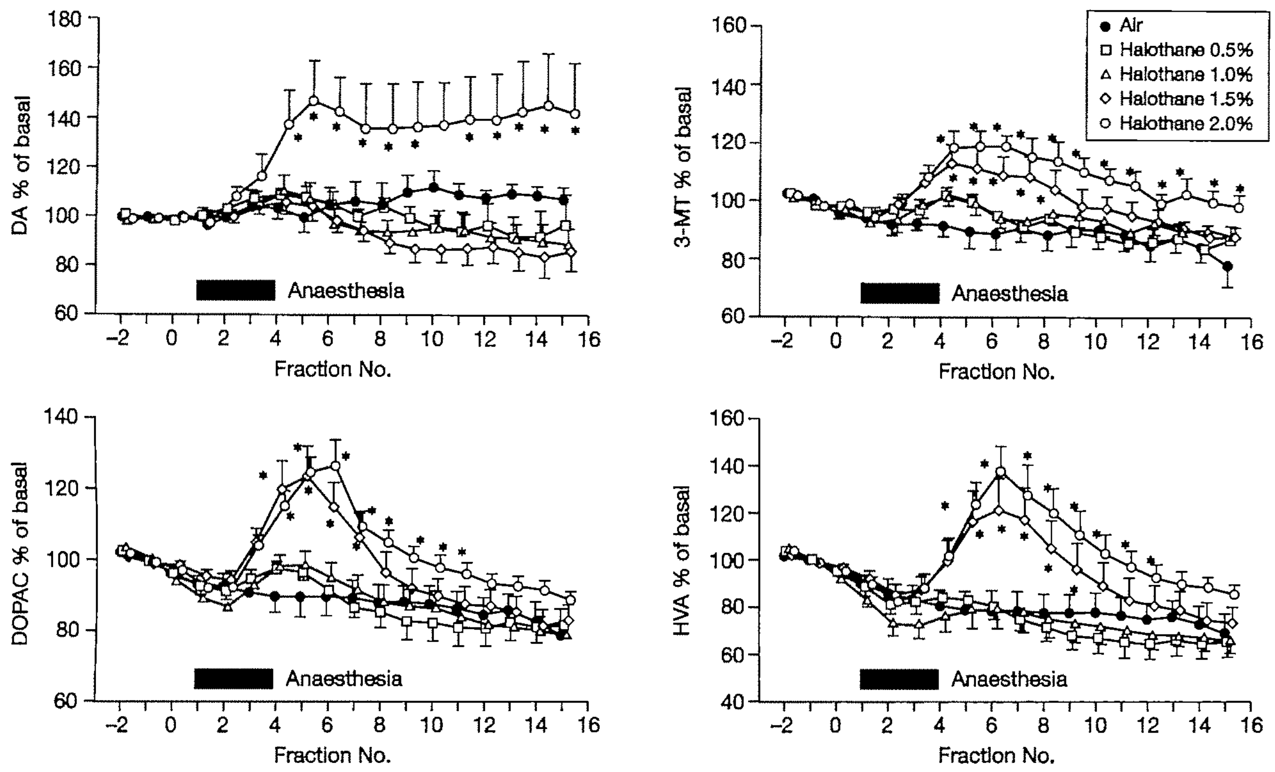

Fig 1 Effect of halothane anaesthesia on concentrations of extracellular dopamine and its metabolites (3-MT, DOPAC and HVA). In this and following figures, the ordinate of each graph shows the level of dopamine or its metabolites expressed as the percentage of the baseline concentration, which is the mean of three consecutive values immediately before the start of halothane anaesthesia; each point is the mean (SEM) (n=6); dialysate fractions were obtained every 20 min. Asterisks indicate significant changes (P<0.05; Newman–Keuls *post hoc* comparison) compared with the control value at the corresponding time point.

Experiment 3

Local application of methamphetamine and nomifensine was tested. Methamphetamine and nomifensine were dissolved in Ringer solution to give a concentration of 5 µmol litre^{-1}. At least six dialysate samples were obtained before starting an experiment and perfusate was changed from standard Ringer solution to solution containing methamphetamine or nomifensine. The time that pretreatment began will be hereafter termed 'Fr. -3' (fraction -3). Starting 80 min after Fr. 1, the rat received air or 0.5 or 1.5% halothane for 1 h.

Statistical analysis

Data were analysed by two-way analysis of variance with drugs as a between-subjects variable and time as a within-subject variable. For each drug with a significant (P<0.05) drug–time interaction, analysis included one-way analysis of variance followed by Newman–Keuls *post hoc* comparison (NCSS 2000, Kaysville, UT, USA).

Drugs

Halothane was obtained from Takeda Chemical Industries (Osaka, Japan), Methamphetamine from Dainippon Pharmaceutical (Osaka, Japan) and Nomifensine from ICN Pharmaceuticals (Costa Mesa, CA, USA).

Results

In control experiments, the predrug dialysate concentrations of DA, 3-MT, DOPAC and HVA were 2.25 (SEM 0.26), 3.25 (0.20), 1085 (138) and 393 (23) nM respectively. The concentration of DA increased gradually from 99.1 (1.4) to 108.4 (4.7)% throughout the experiments (from Fr. 0 to Fr. 15), while the concentrations of DA metabolites decreased from 96.1 (1.6) to 78.4 (7.0)% for 3-MT, from 96.7 (1.4) to 79.2 (7.6)% for DOPAC, and from 96.2 (2.0) to 69.9 (8.5)% for HVA. These trends, which have also been observed by others$^{9\ 11-14}$, are considered to be common in microdialysis experiments on DA dynamics. In the present study, the above changes in concentrations of DA and its metabolites were taken as the baseline with which drug-induced changes were compared.

Effect of halothane anaesthesia

As shown in Fig. 1, the induction of halothane anaesthesia did not change the concentration of DA except in the 2% halothane group. In contrast, all concentrations of halothane studied (0.5, 1.0, 1.5 and 2%) increased the concentrations

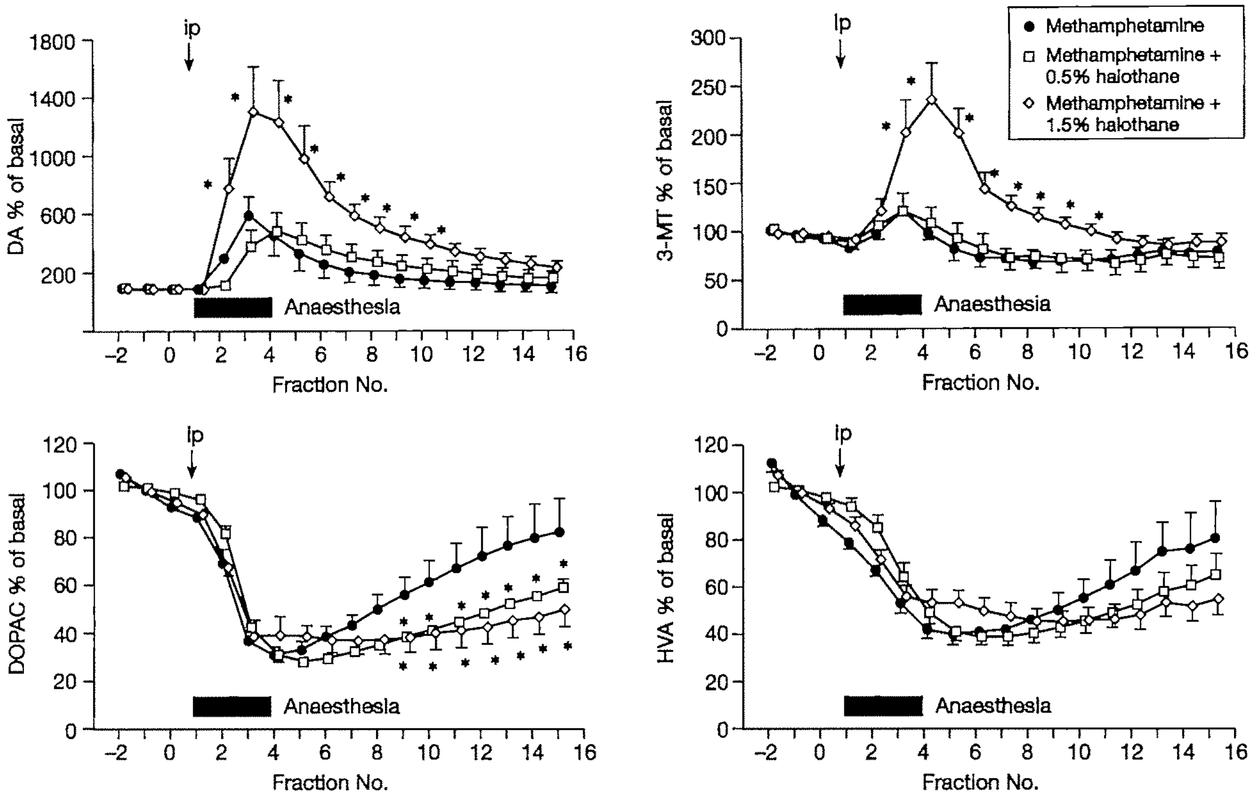

Fig 2 Effects of systemically administered methamphetamine 2 mg kg^{-1} on the concentrations of extracellular dopamine and its metabolites with or without halothane anaesthesia. Asterisks indicate significant changes ($P<0.05$; Newman–Keuls *post hoc* comparison) compared with the control value (without anaesthesia) at the corresponding time point.

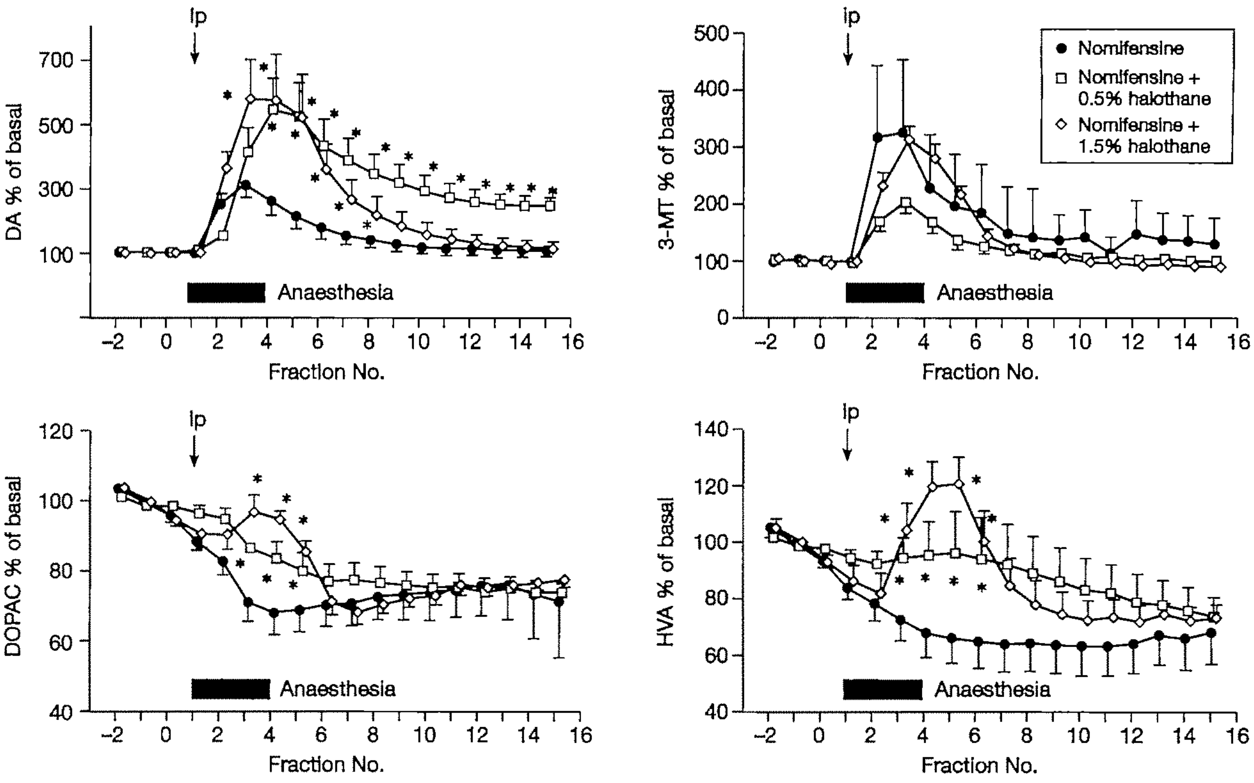

Fig 3 Effects of locally administered methamphetamine (2 mg kg^{-1}) on the concentrations of extracellular dopamine and its metabolites with and without halothane anaesthesia. Asterisks indicate significant changes ($P<0.05$; Newman–Keuls *post hoc* comparison) compared with the control value (without anaesthesia) at the corresponding time point.

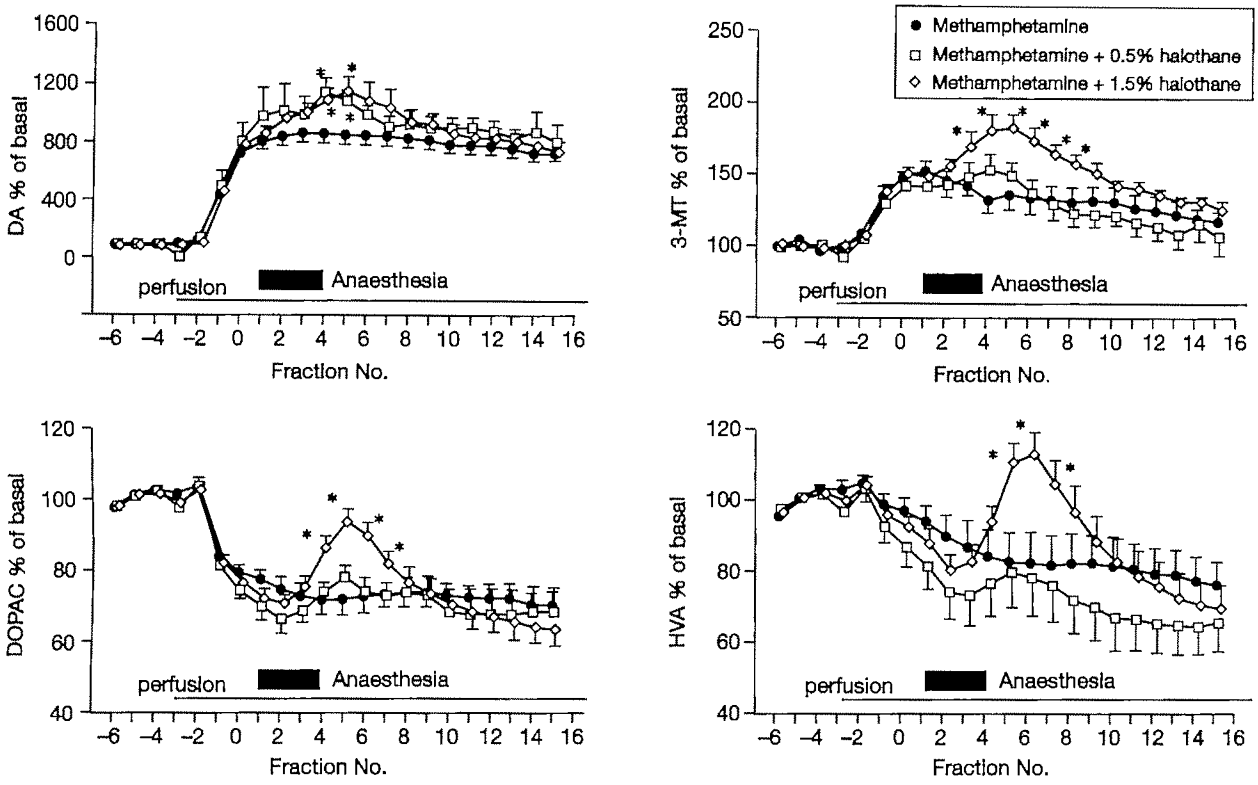

Fig 4 Effects of systemically administered nomifensine (10 mg kg^{-1}) on the concentrations of extracellular dopamine and its metabolites with and without halothane anaesthesia. Asterisks indicate significant changes ($P<0.05$; Newman–Keuls *post hoc* comparison) compared with the control value (without anaesthesia) at the corresponding time point.

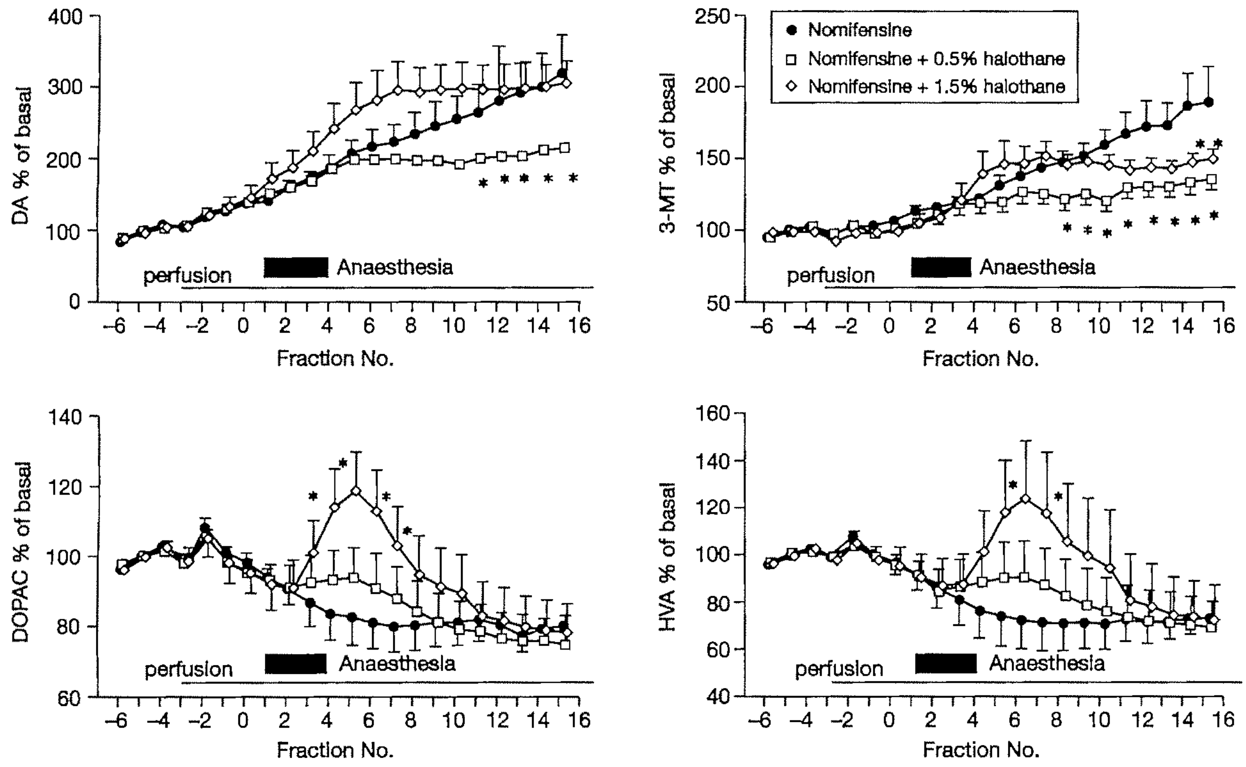

Fig 5 Effects of locally administered nomifensine (10 mg kg^{-1}) on the levels of extracellular dopamine and its metabolites with and without halothane anaesthesia. Asterisks indicate significant changes ($P<0.05$; Newman–Keuls *post hoc* comparison) compared with the control value (without anaesthesia) at the corresponding time point.

of 3-MT and DOPAC in a dose-dependent manner. Halothane at concentrations less than 1.5% failed to increase HVA. During the 4-h recovery period from anaesthesia, the concentrations of DA metabolites recovered to baseline levels with a delay, but 2% halothane induced a sustained increase in DA concentration that did not recover until the end of the experiment.

Effect of halothane on rats treated with methamphetamine or nomifensine

Systemically administered methamphetamine 2 mg kg^{-1} or nomifensine 10 mg kg^{-1} markedly increased the concentrations of DA and 3-MT in striatal dialysates, the effect lasted 2.5 h (Figs 2 and 4). After intraperitoneal administration of methamphetamine, the dialysate concentrations of DOPAC and HVA were decreased by 90%. This is consistent with the known ability of methamphetamine to enter the nerve terminals and inhibit monoamine oxidase (MAO).[15] When anaesthesia was with 0.5 or 1.5% halothane, i.e. concentrations that failed to increase the extracellular concentration of DA, the effect of nomifensine was strongly potentiated. Halothane anaesthesia increased DOPAC and HVA in nomifensine-pretreated rats but failed to influence DOPAC and HVA in methamphetamine-pretreated rats.

Locally administered methamphetamine increased the extracellular concentrations of DA and 3-MT and decreased those of DOPAC and HVA. Locally administered nomifensine caused a gradual increase in DA and 3-MT concentrations (Fig. 5). Halothane anaesthesia failed to affect this change, whereas 1.5% halothane increased DOPAC and HVA concentrations. Halothane 1.5% significantly increased the extracellular concentrations of DA metabolites, including 3-MT, DOPAC and HVA when methamphetamine or nomifensine was administered locally (Figs 3 and 5).

Discussion

The aim of the present study was to elucidate in detail the site and the mode of action of halothane anaesthesia on the concentrations of extracellular DA and its metabolites in the striatum of the rat using *in vivo* microdialysis techniques under different experimental conditions. To this end, methamphetamine, a widely abused drug, and nomifensine, a selective DA uptake blocker, were administered systemically or locally, thereby increasing the extracellular concentration of DA in two ways: methamphetamine, like amphetamine, releases DA from the cytoplasm into the extracellular space[16 17] and nomifensine prevents the reuptake of DA already present in the extracellular space.[18–20] DA concentrations in *in vivo* microdialysis experiments are known to be affected by many factors, including the period of time after probe implantation,[11 12] the type of perfusion medium[21 22] and animal stress.[13 14]

Although the effects of halothane anaesthesia on the concentrations of extracellular DA and its metabolites[1–5 23 24] and on acetylcholine release and transmitter metabolism[25–27] have been studied by several authors, no consensus about the mechanism of action of halothane anaesthesia has been reached. Osborne *et al.*[2] and Stahle *et al.*[3] have reported increases in the extracellular concentration of DA in the rat striatum during halothane anaesthesia, whereas Fink-Jensen *et al.*[5] have found no change in DA. Miyano *et al.*[4] investigated the dose-dependency of halothane on the concentrations of DA and its metabolites, and showed that anaesthesia increases DA and DOPAC concentrations during inhalation of 2% halothane. In our experiments, the extracellular concentration of DA was unchanged during halothane anaesthesia except when it was used at an extremely high concentration (2%). The DA metabolites in the dialysate, including 3-MT, DOPAC and HVA, were increased by halothane inhalation. Our results and those of other investigators are consistent: halothane <2.0% does not change the concentration of extracellular DA; however, at concentrations of ⩾2.0%, halothane increases extracellular DA.

Miyano *et al.*[4] and Fink-Jensen *et al.*[5] have suggested that halothane may cause respiratory depression and subsequent brain hypoxia, thereby increasing extracellular DA. In the central nervous system, severe hypoxia followed by ischaemia increases the extracellular concentrations of different transmitters, including DA,[28–30] by leakage from damaged axons.[31 32] Therefore, our experiments suggest that halothane at high concentrations might cause secondary damage to neurones as a result of either hypoxia induced by respiratory depression or ischaemia induced by circulatory depression. During hypoglycaemia, the drop in intracellular ATP might cause inhibition of the sodium pump and the accumulation of $[Na^+]_i$,[33] resulting in the reverse operation of DA transporters, leading to DA release. This release is $[Ca^{2+}]_o$-independent and not affected by neuronal firing.[34 35] In our previous investigation,[9] the observation that halothane anaesthesia induced hypercapnia suggested a state of respiratory depression.

In another series of experiments, we investigated the effect of halothane on methamphetamine- and nomifensine-induced changes in the extracellular DA concentration. Nomifensine is a DA reuptake inhibitor[18 20] and has been reported to increase the extracellular DA concentration, concentrations of DOPAC and HVA remaining unchanged.[36–39] Nomifensine prevents the uptake of DA released primarily from non-synaptic varicosites[34 39] in response to axonal activity, thereby increasing DA concentration in the extracellular space. In the present study, halothane anaesthesia potentiated the increase in extracellular DA induced by systemically administered nomifensine, whereas it failed to enhance the increase of DA when nomifensine was administered locally in the perfusate. Augmentation of anaesthesia-induced DA release by DA reuptake inhibitors had been reported by Opacka-

Juffry *et al.*[1] for isoflurane and nomifensine and by Fink-Jensen *et al.*[5] for halothane and vanoxerine. They have suggested that volatile anaesthetics might increase the rate of release of DA, but is then compensated for by increased reuptake activity at axon terminals.[1 5] However, the results of the present investigation reveal that DA release from axon terminals in the striatum of rats is not activated by halothane when the reuptake process is inhibited by local administration of nomifensine. Therefore, it should be concluded that it is the enhanced neural activity induced by halothane that potentiates the effect of the reuptake inhibitor on DA release rather than some additional effect of volatile anaesthetics at nerve endings.

Methamphetamine is a widely abused drug that, like amphetamine, is able to release DA. Amphetamine has been reported to increase the concentration of extracellular DA and 3-MT but to decrease the concentrations of DOPAC and HVA.[6 37 40 41] DOPAC, a major metabolite of DA present in the cytoplasm, is readily metabolized by MAO.[37 42 43] Methamphetamine releases DA from a cytoplasmic pool, which is the major source of substrate for the metabolizing enzyme, monoamine oxidase, MAO.[7] Halothane anaesthesia at concentrations (0.5 and 1.5%) at which the extracellular concentration of DA is not increased, potentiated the ability of methamphetamine to induce DA release [without induction of anaesthesia there was a 3-fold increase, but with halothane there was a 13-fold increase (Fig. 2)]. Methamphetamine reduced the concentrations of DOPAC and HVA when administered either systemically or locally, whereas increases in DOPAC and HVA in response to halothane anaesthesia were found only when methamphetamine was administered locally. However, the results of the present investigation reveal that methamphetamine might reduce DA not only at an axon terminal but also at other neuronal pathways, because locally administered methamphetamine did not prevent the increase in DOPAC induced by halothane, suggesting that halothane modifies DA metabolism in axon terminals.

Our findings argue against the possibility that halothane acts directly on the DA transporters, at least at concentrations less than 2%. At concentrations higher than 1.5% effects of halothane on the transporter cannot be excluded. Previous *in vitro* studies with rat brain synaptosomes support this conclusion. In these experiments, halothane inhibited DA uptake,[23 24] and either increased[23] or did not alter[24] the release of DA from synaptosomes. If halothane were indeed a DA reuptake inhibitor, as indicated by *in vitro* studies,[23 24] the effects of nomifensine in our experiments should have been further increased. However, except at the highest concentration (2%), this was not the case.

With systemic administration of methamphetamine or nomifensine, we demonstrated that 1.5% halothane potentiated the methamphetamine-induced increase in DA concentration. In addition, the increase in 3-MT induced by methamphetamine, but not nomifensine, was enhanced by halothane anaesthesia. The observation that the 3-MT concentration was increased in methamphetamine-pretreated rats suggests that halothane also alters DA metabolism at postsynaptic sites, because 3-MT is a catabolic product of the postsynaptic enzyme, catechol-*o*-methyltransferase.[44–47] Differences observed between the effects of methamphetamine and nomifensine on DA release and metabolism support the conclusion that halothane modifies the metabolism of DA in neural transmission pathways.

In conclusion, the present study clearly shows that halothane anaesthesia increases the concentrations of extracellular DA metabolites in the rat striatum, whereas the concentration of DA remains changed. Halothane augmented methamphetamine- and nomifensine-induced increases in extracellular DA concentration when the drugs were administered systemically. These findings suggest that potentiation of DA release by halothane anaesthesia results from increased neural activity in the nigrostriatal pathway rather than from modulation of DA release or DA reuptake at axon terminals. Excessive release of DA may produce striatal neurotoxicity.[48 49] This suggests that halothane potentially affects neuronal firing in the dopaminergic pathway of the rat striatum, at least in the context of excessive release, reuptake and metabolism of DA. Because the striatum is part of the limbic system, it seems likely that halothane anaesthesia has similar effects in the rest of the limbic system, e.g. the nucleus accumbens. Therefore, the use of this type of anaesthesia in patients who are drug abusers may be problematical.[50 51]

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References

1 Opacka-Juffry J, Ahier RG, Cremer JE. Nomifensine-induced increase in extracellular striatal dopamine is enhanced by isoflurane anaesthesia. *Synapse* 1991; **7**: 169–71

2 Osborne PG, O'Connor WT, Drew KL, Ungerstedt U. An *in vivo* microdialysis characterization of extracellular dopamine and GABA in dorsolateral striatum of awake freely moving and halothane anaesthetised rats. *J Neurosci Methods* 1990; **34**: 99–105

3 Stahle L, Collin AK, Ungerstedt U. Effects of halothane anaesthesia on extracellular levels of dopamine, dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindolacetic acid in rat striatum: a microdialysis study. *Naunyn-Schmiedebergs Arch Pharmacol* 1990; **342**: 136–40

4 Miyano K, Tanifuji Y, Eger EI II. The effect of halothane dose on striatal dopamine: an *in vivo* microdialysis study. *Brain Res* 1993; **605**: 342–4

5 Fink-Jensen A, Ingwersen SH, Nielsen PG. Halothane anesthesia

enhances the effect of dopamine uptake inhibition on interstitial levels of striatal dopamine. *Naunyn-Schmiedebergs Arch Pharmacol* 1994; **350**: 239–44

6 Butcher SP, Fairbrother IS, Kelly JS, Arbuthnott GW. Amphetamine-induced dopamine release in the rat striatum: an *in vivo* microdialysis study. *J Neurochem* 1988; **50**: 346–55.

7 Parker EM, Cubeddu LX. Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. *J Pharmacol Exp Ther* 1986; **237**: 179–92

8 Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*, 4th Edn. San Diego, CA: Academic Press, 1998

9 Adachi Y, Uchihashi Y, Watanabe K, Satoh T. Halothane anesthesia decreases the extracellular level of dopamine in rat striatum: a microdialysis study *in vivo*. *J Anesth* 2000; **14**: 82–90

10 Sato K, Windissch K, Matko I, Vizi ES. Effects of non-depolarizing neuromuscular blocking agents on norepinephrine release from human atrial tissue obtained during cardiac surgery. *Br J Anaesth* 1999; **82**: 904–9

11 Drew KL, O'Connor WT, Kehr J, Ungerstedt U. Characterisation of gamma aminobutyric acid and dopamine overflow following acute implantation of a microdialysis probe. *Life Sci* 1989; **45**: 1307–17

12 Osborne PG, O'Connor WT, Kehr J, Ungerstedt U. *In vivo* characterisation of extracellular dopamine, GABA and acetylcholine from the dorsolateral striatum of awake freely moving rats by chronic microdialysis. *J Neurosci Methods* 1991; **37**: 93–102

13 Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ. Differential effect of stress on *in vivo* dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *J Neurochem* 1989; **52**: 1655–8

14 Feenstra MGP, Botterblom MHA. Rapid sampling of extracellular dopamine in the rat prefrontal cortex during food consumption, handling and exposure to novelty. *Brain Res* 1996; **742**: 17–24

15 Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol* 1993; **33**: 639–77

16 Butcher SP, Fairbrother IS, Kelly JS, Arbuthnott GW. Amphetamine-induced dopamine release in the rat striatum: an *in vivo* microdialysis study. *J Neurochem* 1988; **50**: 346–55

17 Fumagalli F, Gainetdinov RR, Valenzano KJ, Caron MG. Role of dopamine transporter in methamphetamine-induced neurotoxicity: evidence from mice lacking the transporter. *J Neurosci* 1998; **18**: 4861–9

18 Lee HJ, Alcorn LM, Weiler MH. Effects of various experimental manipulations on neostriatal acetylcholine and dopamine release. *Neurochem Res* 1991; **16**: 875–83

19 Butcher SP, Liptrot J, Arbuthnott GW. Characterisation of methylphenidate and nomifensine induced dopamine release in rat striatum using *in vivo* brain microdialysis. *Neurosci Lett* 1991; **122**: 245–8

20 Church WH, Justice JB Jr, Byrd LD. Extracellular dopamine in rat striatum following uptake inhibition by cocaine, nomifensine and benztropine. *Eur J Pharmacol* 1987; **139**: 345–8

21 Osborne PG, O'Connor WT, Ungerstedt U. Effect of varying the ionic concentration of a microdialysis perfusate on basal striatal dopamine levels in awake rats. *J Neurochem* 1991; **56**: 452–6

22 Chen NNH, Lai Y, Pan WHT. Effects of different perfusion medium on the extracellular basal concentration of dopamine in striatum and medial prefrontal cortex: a zero-net flux microdialysis study. *Neurosci Lett* 1997; **225**: 197–200

23 El-Maghrabi EA, Eckenhoff RG. Inhibition of dopamine transport in rat brain synaptosomes by volatile anesthetics. *Anesthesiology* 1993; **78**: 750–6

24 Mantz J, Varlet C, Lecharny J, Henzel D, Lenot P, Desmonts J. Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. *Anesthesiology* 1994; **80**: 352–63

25 Gomez RS, Gomez MV, Prado MAM. The effect of isoflurane on the release of [^{3}H]-acetylcholine from rat brain cortical slices. *Brain Res Bull* 2000; **52**: 263–7

26 Gomez RS, Guatimosim C, Massensini A, Gomez MV, Prado MAM. The effect of halothane on cytosolic free calcium concentration of SN56 cells. *Br J Anaesth* 1999; **82**: 91–2

27 Griffiths R, Norman RI. Effects of anaesthetics on uptake, synthesis and release of transmitters. *Br J Anaesth* 1993; **71**: 96–107

28 Nakai T, Milusheva E, Baranyi M, Uchihashi Y, Satoh T, Vizi ES. Excessive release of [^{3}H] noradrenaline and glutamate in response to simulation of ischemic condition in rat spinal cord slice preparation: effect of NMDA and AMPA receptor antagonists. *Eur J Pharmacol* 1999; **366**: 143–50.

29 Uchihashi Y, Bencsics A, Umeda E, Nakai T, Sato T. Na$^+$ channel block prevents the ischemia-induced release of norepinephrine from spinal cord slices. *Eur J Pharmacol* 1998; **346**: 145–50

30 Milusheva E, Doda M, Pasztor E, Lajtha A, Sershen H, Vizi ES. Regulatory interactions among axon terminals affecting the release of different transmitters from rat striatal slices under hypoxic and hypoglycemic conditions. *J Neurochem* 1992; **59**: 946–52

31 Koorn R, Kahn RA, Brannan TS, Martinez-Tica J, Weinberger J, Reich DL. Effect of isoflurane and halothane on *in vivo* ischemia-induced dopamine release in the corpus striatum of the rat. *Anesthesiology* 1993; **79**: 827–35

32 Warner DS, McFarlane C, Todd MM, Ludwig P, McAllister AM. Sevoflurane and halothane reduce focal ischemic brain damage in the rat. *Anesthesiology* 1993; **79**: 985–92

33 Milusheva EA, Doda M, Baranyi M, Vizi ES. Effect of hypoxia and glucose deprivation on ATP level, adenylate energy charge and [Ca^{2+}]$_o$-dependent and independent release of [^{3}H] dopamine in rat striatal slices. *Neurochem Int* 1996; **28**: 501–7

34 Vizi ES. Role of high-affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. *Pharmacol Rev* 2000; **52**: 63–81

35 Adam-Vizi V. External Ca^{2+}-independent release of neurotransmitters. *J Neurochem* 1992; **58**: 395–405

36 Zetterstrom T, Sharp T, Collin AK, Ungerstedt U. *In vivo* measurement of extracellular dopamine and DOPAC in rat striatum after various dopamine-releasing drugs: implications for the origin of extracellular DOPAC. *Eur J Pharmacol* 1988; **148**: 327–34

37 Hurd YL, Ungerstedt U. *In vivo* neurochemical profile of dopamine uptake inhibitors and releasers in rat caudate-putamen. *Eur J Pharmacol* 1989; **166**: 251–60

38 Hurd YL, Ungerstedt U. Ca^{2+} dependence of the amphetamine, nomifensine, and Lu 19-005 effect on *in vivo* dopamine transmission. *Eur J Pharmacol* 1989; **166**: 261–9

39 Kiss JP, Hennings EC, Zsilla G, Vizi ES. A possible role of nitric oxide in the regulation of dopamine transporter function in the striatum. *Neurochem Int* 1999; **34**: 345–50

40 Parker EM, Cubeddu LX. Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. *J Pharmacol Exp Ther* 1986; **237**: 179–92

41 Parker EM, Cubeddu LX. Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. II. Release in the presence of vesicular transmitter stores. *J Pharmacol Exp Ther* 1986; **237**: 192–203

42 Jones SR, Gainetdinov RR, Jaber M, Giros B, Wightman RM, Caron MG. Profound neuronal plasticity in response to inactivation of the dopamine transporter. *Proc Natl Acad Sci USA* 1998; **95**: 4029–34

43 Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J Neurosci* 1998; **18**: 1979–86

44 Kaplan GP, Hartman BK, Creveling CR. Immunohistochemical demonstration of catechol-o-methyltransferase in mammalian brain. *Brain Res* 1979; **167**: 241–50

45 Westerink BHC, Spaan SJ. On the significance of endogenous 3-methoxytyramine for the effects of centrally acting drugs on dopamine release in the rat brain. *J Neurochem* 1982; **38**: 680–6

46 Sailer CF, Salama AI. 3-Methoxytyramine accumulation: effects of typical neuroleptics and various atypical compounds. *Naunyn-Schmiedebergs Arch Pharmacol* 1986; **334**: 125–32

47 Kaakkola S, Wurtman RJ. Effects of COMT inhibitors on striatal dopamine metabolism: a microdialysis study. *Brain Res* 1992; **587**; 241–9

48 Cadet JL, Brannock C. Free radicals and the pathobiology of brain dopamine systems. *Neurochem Int* 1998; **32**: 117–31

49 Wrona MZ, Yang Z, Zhang F, Dryhurst G. Potential new insights into the molecular mechanisms of methamphetamine-induced neurodegeneration. *NIDA Res Monogr* 1997; **173**: 146–74

50 Rittoo DB, Rittoo D. Complications of 'ecstacy' misuse. *Lancet* 1992; **340**: 725–6

51 Fischer SP, Healzer JM, Brook MW, Brock-Utne JG. General anesthesia in a patient on long-term amphetamine therapy: is there cause for concern? *Anesth Analg* 2000; **91**: 758–9

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Lidocaine reduces ischaemic but not reperfusion injury in isolated rat heart

D. Ebel[1]*, P. Lipfert[2], J. Fräßdorf[2], B. Preckel[2], J. Müllenheim[2], V. Thämer[1] and W. Schlack[2]

[1]Physiologisches Institut I, Abteilung für Herz- und Kreislaufphysiologie, Heinrich-Heine-Universität Düsseldorf, Postfach 10 10 07, D-40001 Düsseldorf, Germany. [2]Institut für Klinische Anaesthesiologie, Heinrich-Heine-Universität Düsseldorf, Germany

**Corresponding author*

The local anaesthetic lidocaine protects the myocardium in ischaemia–reperfusion situations. It is not known if this is the consequence of an anti-ischaemic effect or an effect on reperfusion injury. Therefore, we investigated the effect of two concentrations of lidocaine on myocardial ischaemia–reperfusion injury and on reperfusion injury alone. We used an isolated rat heart model where heart rate, ventricular volume and coronary flow were kept constant. Hearts underwent 45 min of low-flow ischaemia followed by 90 min reperfusion. Two groups received lidocaine 1.7 or 17 µg ml^{-1} starting 5 min before the onset of reperfusion. In two additional groups, lidocaine infusion started 5 min before low-flow ischaemia. In all groups, lidocaine administration was stopped after 15 min of reperfusion. One group served as an untreated control (n=11 in each group). Left ventricular developed pressure (LVDP) and total creatine kinase release (CKR) were measured. Lidocaine administration during ischaemia and reperfusion led to an improved recovery of LVDP during reperfusion (1.7 µg ml^{-1}, 54 (SEM 10) mm Hg; 17 µg ml^{-1}, 71 (9) mm Hg at 30 min of reperfusion; both significantly different from control (21 (4) mm Hg) (P<0.05)) and a reduced CKR (1.7 µg ml^{-1}, 79 (13) IU; 17 µg ml^{-1}, 52 (8) IU at 30 min of reperfusion; both significantly different from control (130 (8) IU (P<0.05)). Lidocaine given during early reperfusion only, affected neither LVDP during reperfusion (1.7 µg ml^{-1}, 19 (6) mm Hg (P=1.0); 17 µg ml^{-1}, 36 (8) mm Hg (P=0.46)) nor CKR (156 (21) IU (P=0.50) and 106 (14) IU (P=0.57)). We conclude that lidocaine protects the myocardium against ischaemic but not against reperfusion injury in the isolated rat heart.

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Myocardial ischaemia can lead to cellular damage, not only during ischaemia itself, but also during subsequent reperfusion. Reperfusion injury can be reduced by modifying conditions of reperfusion.[1] One major aim of therapy for myocardial ischaemia is to limit infarct size by restoring coronary blood flow.[2] Several drugs reduce myocardial ischaemia–reperfusion injury further. When administering these drugs, it is important to know if they are protective only when given during ischaemia or if they are still protective when given after ischaemia during reperfusion. An example is the volatile anaesthetic halothane, which has greater protective effect against reperfusion injury than against ischaemic injury in isolated hearts.[3]

Lidocaine is often used as an anti-arrhythmic drug in ischaemia–reperfusion situations. Besides having anti-arrhythmic effects, lidocaine may protect myocardium not only against ischaemic but also against reperfusion injury by affecting intracellular concentrations of sodium[4 5] and calcium[6 7] during ischaemia and reperfusion, by protecting cellular membranes against long-chain acylcarnitines[8] and reactive oxygen species,[9] and perhaps by blocking calcium channels.[10 11] Lidocaine reduces myocardial ischaemia–reperfusion injury in isolated rat heart[12–14] and *in vivo* (in rabbit,[15] cat,[16] pig,[17 18] and dog[19–22]).

In all these studies, lidocaine administration started before or early during ischaemia. The question whether the cardioprotective effect of lidocaine is a consequence of

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anti-ischaemic properties or whether lidocaine can reduce myocardial reperfusion injury could not be answered by these studies. The present study was designed to determine if lidocaine reduces ischaemic or reperfusion injury, or both.

We used an isolated rat heart model with 45 min of low-flow ischaemia and 90 min of reperfusion. A clinically relevant concentration of lidocaine and a 10-fold higher concentration were administered either during ischaemia and early reperfusion or during early reperfusion alone.

Methods

The study was performed in accordance with the regulations of the German Animal Protection Law and local institutional regulations.

Preparation of the isolated rat heart model used in this study has been described in detail previously.[3] In brief, isolated hearts from male Wistar rats were perfused in a Langendorff preparation with Krebs–Ringer solution at a constant flow rate of 14 ml min^{-1}. Heart rate was maintained at 374 beats min^{-1}. For measurement of left ventricular pressure (LVP), a latex balloon (size no. 5; Hugo Sachs Elektronik, March, Germany) was introduced into the left ventricle via the cut mitral valve. The balloon was fixed at the tip of a stainless steel cannula which was connected directly to a P23 pressure transducer (Gould, Cleveland, OH, USA). At the beginning of each experiment, the latex balloon was filled, air-bubble free, with Krebs–Henseleit buffer resulting in a left ventricular end-diastolic pressure (LVEDP) of 10–12 mm Hg, and the volume was kept constant throughout the experiment. Coronary perfusion pressure (CPP) was also measured using a Gould P23 pressure transducer. Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled and further processed in order to determine myocardial oxygen consumption and creatine kinase (CK) activity at different times during the experimental course, as markers of cellular damage. Total cumulative CK release was assessed by determining area under the curve.

Experimental protocol

Figure 1 shows the experimental protocol used for the different groups. After preparation, a stabilization period of 20 min was allowed. Baseline measurements were then performed. Low-flow ischaemia was initiated by reducing coronary flow from 14 to 0.5 ml min^{-1} and maintained for 45 min; 90 min of reperfusion (14 ml min^{-1}) followed. Samples for measurement of CK activity were collected 5 min before low-flow ischaemia, immediately before low-flow ischaemia, after 20, 30 and 40 min of ischaemia, and 1, 3, 5, 10, 15, 20, 30, 45, 60 and 90 min after the onset of reperfusion.

Five groups (n=11 in each) and two lidocaine concentrations (1.7 and 17 µg ml^{-1}) were studied. To achieve lidocaine concentrations of 1.7 or 17 µg ml^{-1} in the perfusate of lidocaine-treated hearts, a 100-fold higher concentration (0.17 or 1.7 mg ml^{-1}) was infused with a hundredth of the total flow (Model 5003 infusion pump; Precidior Infors, Basel, Switzerland). In two groups, the two lidocaine concentrations were administered during the last 5 min of low-flow ischaemia and during the first 15 min of reperfusion. In two further groups, lidocaine infusion was started 5 min before low-flow ischaemia and stopped after 15 min of reperfusion. One group served as an untreated control.

Data analysis and statistics

LVP and CPP were continuously recorded on an ink recorder (Mark 260; Gould). The data were digitized using an analogue-to-digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and processed on a personal computer. Twenty sequential cardiac cycles were averaged to compensate for variations. Left ventricular developed pressure (LVDP) as a variable of myocardial contractility was calculated by subtracting LVEDP from left ventricular systolic pressure. All data are expressed as mean (SEM).

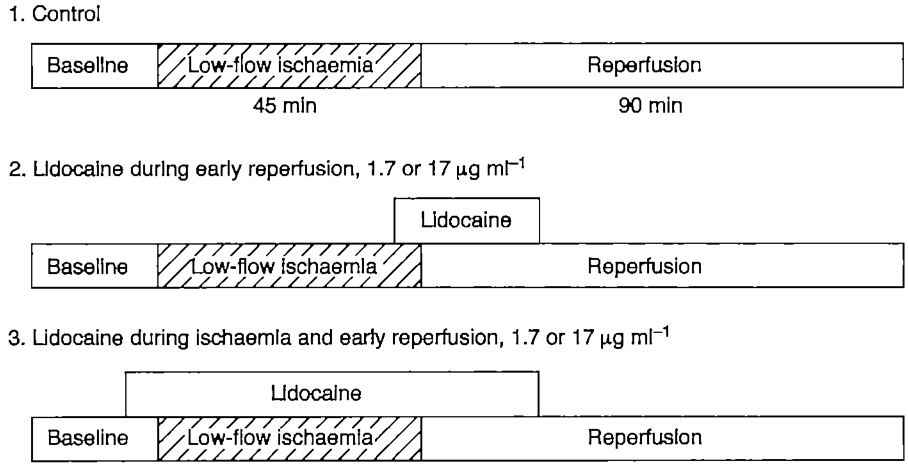

Fig 1 Experimental protocol.

For haemodynamic variables and myocardial oxygen consumption, statistical analysis was performed using analysis of variance (ANOVA). If ANOVA showed a group effect, Dunnett's test was used as a *post hoc* test at each measurement time. To detect group differences in cumulative CK release, ANOVA and Dunnett's *post hoc* test were performed. In the groups that received lidocaine during ischaemia and reperfusion, the pre-ischaemic effect of lidocaine was assessed using Student's *t*-test for paired values. All statistical calculations were performed with the original data; *P*-values of <0.05 were regarded as significant.

Results

A total of 55 hearts, fulfilling predefined quality criteria (LVDP >80 mm Hg at CPP <100 mm Hg, and no ventricular fibrillation during the stabilization period), were included. CK samples for one heart in the control group were lost; all other data sets were complete. Heart weight was similar in all groups (1.14 (0.02) g, P=0.47–1.0 *vs* control).

Haemodynamic function

Under baseline conditions, haemodynamic variables were similar in all groups. Figure 2 shows LVDP (top), LVEDP (middle) and oxygen consumption during the course of the experiment. Tables 1–3 show CPP and left ventricular d*P*/d*t*.

Administration of lidocaine 1.7 µg ml^{-1} before ischaemia had no significant effect on any haemodynamic variable, while lidocaine 17 µg ml^{-1} reduced LVDP and d*P*/dt_{max} by 11 (2)% (P<0.01) and increased d*P*/dt_{min} by 9 (1)% (P<0.05) and CPP by 19 (6)% (not statistically significant, P=0.17).

During low-flow ischaemia, LVDP was similarly reduced in all groups, to 4.2 (0.3)% of baseline (P<0.001 *vs* baseline). In the control group and the groups that received lidocaine only during early reperfusion, LVDP recovered only slightly during reperfusion (control, 19.7 (3.4)% of baseline; 1.7 µg ml^{-1}, 18.2 (6.4)% of baseline; 17 µg ml^{-1}, 31.7 (6.7) % of baseline; after 30 min of reperfusion). Recovery of LVDP in the groups receiving lidocaine during ischaemia and reperfusion was significantly improved (1.7 µg ml^{-1}, 60.3 (11.8)% of baseline, P=0.012; 17 µg ml^{-1}, 69.6 (10.3)% of baseline, P<0.001 *vs* control; after 30 min reperfusion). LVEDP increased during low-flow ischaemia in the control group and the groups that received lidocaine only during reperfusion (control, 272 (34)% of baseline; 1.7 µg ml^{-1}, 251 (23)% of baseline; 17 µg ml^{-1}, 320 (55)% of baseline). This increase was smaller in the groups that had received lidocaine during ischaemia and reperfusion (1.7 µg ml^{-1}, 221 (44)% of baseline, P=0.001; 17 µg ml^{-1}, 153 (26)% of baseline, P<0.001 *vs* control). During reperfusion, LVEDP in the groups that received lidocaine during ischaemia and early reperfusion was smaller than that in the control group (control, 528 (65)% of baseline; lidocaine during reperfusion: 1.7 µg ml^{-1}, 605 (91)% of baseline, P=1.0; 17 µg ml^{-1}, 505 (76)% of baseline, P=0.57; lidocaine during ischaemia and reperfusion: 1.7 µg ml^{-1}, 194 (98)% of baseline, P=0.002; 17 µg ml^{-1}, 180 (61)% of baseline, P<0.001 *vs.* control; after 30 min reperfusion).

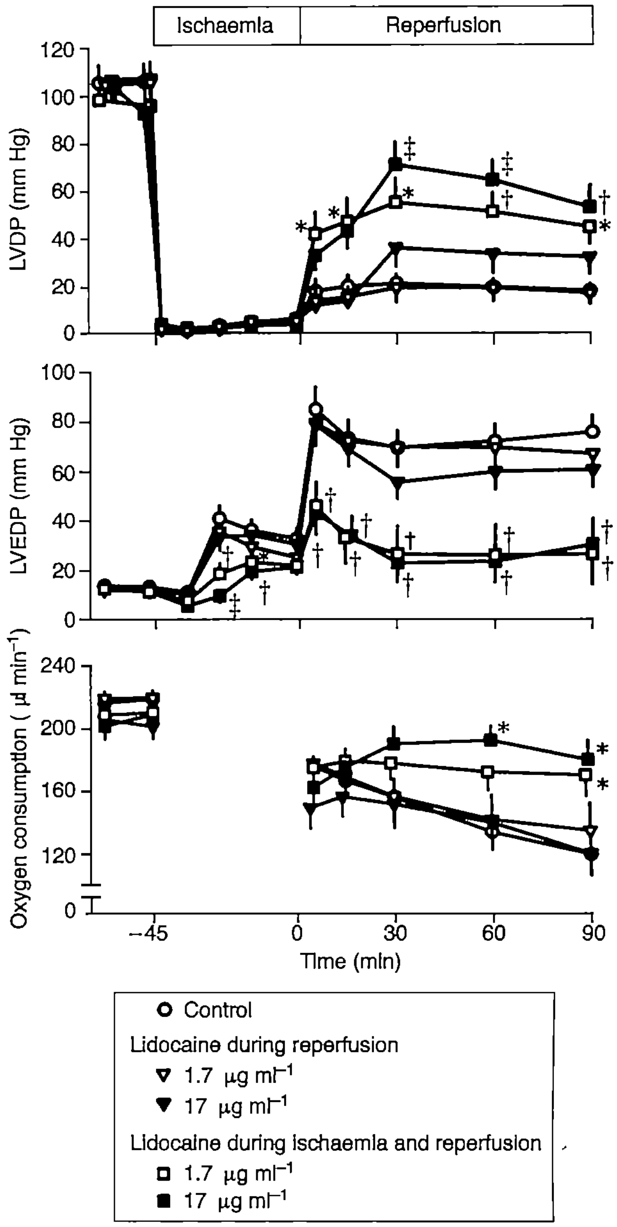

Fig 2 Left ventricular developed pressure (LVDP, top), left ventricular end-diastolic pressure (LVEDP, middle), and myocardial oxygen consumption (bottom) in the five groups. Low-flow ischaemia led to a marked reduction in LVDP and an increase in LVEDP. During reperfusion, LVDP recovered more in the groups that received lidocaine during ischaemia and early reperfusion. In these groups, myocardial oxygen consumption was also higher during reperfusion than in the control group. Data are mean (SEM). *P<0.05, †P<0.01, ‡P<0.001 *vs* control. n=11 in each group.

Myocardial oxygen consumption

Myocardial oxygen consumption is shown in Figure 2 (bottom). After 90 min reperfusion, it was similar in the

Table 1 Coronary perfusion pressure (CPP) during the experimental course. Data are mean (SEM). n=11 in each group. *P<0.05 *vs* control. Coronary flow was 14 ml min^{-1} during baseline and reperfusion, and 0.5 ml min^{-1} during ischaemia

	Control	Lidocaine during reperfusion		Lidocaine during ischaemia and reperfusion	
		1.7 μg ml^{-1}	17 μg ml^{-1}	1.7 μg ml^{-1}	17 μg ml^{-1}
Baseline					
0 min	77 (3)	80 (3)	78 (3)	72 (3)	75 (3)
5 min	80 (4)	81 (3)	81 (4)	76 (3)	90 (7)
Ischaemia					
10 min	9 (1)	10 (1)	8 (1)	10 (2)	9 (1)
20 min	13 (1)	13 (1)	13 (2)	13 (4)	8 (1)
30 min	14 (2)	14 (2)	14 (1)	14 (4)	11 (2)
44 min	13 (2)	14 (2)	15 (1)	14 (4)	12 (1)
Reperfusion					
5 min	100 (5)	106 (7)	100 (4)	85 (5)	85 (5)
15 min	113 (9)	123 (10)	118 (4)	91 (6)	104 (7)
30 min	124 (9)	144 (10)	115 (6)	98 (7)	101 (6)
45 min	140 (10)	161 (11)	128 (9)	105 (9)*	109 (8)
60 min	150 (9)	171 (11)	141 (11)	113 (10)*	117 (9)
90 min	162 (10)	184 (10)	153 (13)	122 (11)*	130 (9)

Table 2 Left ventricular dP/dt_{max} during the experimental course. Data are mean (SEM). n=11 in each group. *P<0.05, †P<0.01 *vs* control; ¶P<0.05 *vs* baseline

	Control	Lidocaine during reperfusion		Lidocaine during ischaemia and reperfusion	
		1.7 μg ml^{-1}	17 μg ml^{-1}	1.7 μg ml^{-1}	17 μg ml^{-1}
Baseline					
0 min	3965 (318)	3767 (204)	3877 (257)	3848 (212)	3923 (190)
5 min	3983 (323)	3808 (212)	3847 (222)¶	3960 (209)	3447 (162)
Ischaemia					
10 min	738 (194)	439 (71)	807 (53)	1176 (285)	889 (88)
20 min	774 (182)	460 (61)	831 (56)	1213 (265)	896 (90)
30 min	804 (195)	528 (58)	837 (57)	1252 (259)	898 (86)
44 min	814 (180)	519 (70)	870 (53)	1254 (252)	922 (91)
Reperfusion					
5 min	1133 (190)	760 (142)	1020 (132)	2248 (431)†	1573 (180)
10 min	1184 (192)	799 (124)	1027 (141)	2394 (468)†	1691 (205)
15 min	1219 (194)	883 (125)	1066 (153)	2576 (509)†	1925 (243)
30 min	1219 (187)	1048 (210)	1693 (258)	2919 (567)†	3172 (380)†
60 min	1204 (218)	991 (191)	1696 (286)	2747 (512)†	2997 (341)†
90 min	1084 (230)	902 (168)	1604 (253)	2585 (470)†	2503 (403)*

control group and the groups that received lidocaine only during early reperfusion (control 54 (6)% of baseline; 1.7 μg ml^{-1}, 61 (8), P=0.86; 17 μg ml^{-1}, 58 (7)% of baseline; P=1.0 *vs* control). In the groups that received lidocaine during ischaemia and reperfusion, myocardial oxygen consumption was significantly higher at the end of the reperfusion period (1.7 μg ml^{-1}, 85 (5)% of baseline, P=0.049; 17 μg ml^{-1}, 85 (5)% of baseline, P=0.014 *vs* control)

Creatine kinase release

Figure 3 shows cumulative CK release as variable of cellular damage. Administration of lidocaine only during early reperfusion had no significant effect on CK release (1.7 μg ml^{-1}, P=0.50; 17 μg ml^{-1}, P=0.57 *vs* control). Lidocaine during ischaemia and early reperfusion reduced CK release by 39.4% (1.7 μg ml^{-1}, P=0.042) and 60.2% (17 μg ml^{-1}, P=0.001) compared with the control group.

Discussion

The cardioprotective effect of lidocaine in ischaemia–reperfusion situations has been demonstrated in several studies. The present study shows that cardioprotection by lidocaine is the consequence of an anti-ischaemic effect, but that lidocaine has no effect on reperfusion injury. Several mechanisms are discussed in the literature that may be responsible for this protective effect:

Reduction of intracellular sodium concentration

Myocardial ischaemia is accompanied by an increase in intracellular sodium concentration ([Na$^+$]$_i$). Sodium influx

Table 3 Left ventricular dP/dt_{min} during the experimental course. Data are mean (SEM). n=11 in each group. *P<0.05, †P<0.01, ‡ P<0.001 *vs* control; ¶P<0.01 *vs* baseline

	Control	**Lidocaine during reperfusion**		**Lidocaine during ischaemia and reperfusion**	
		1.7 μg ml^{-1}	**17 μg ml^{-1}**	**1.7 μg ml^{-1}**	**17 μg ml^{-1}**
Baseline					
0 min	–3071 (264)	–2917 (150)	–2888 (163)	–2917 (174)	–2852 (129)
5 min	–3077 (252)	–2959 (152)	–2912 (140)	–2966 (184)	–2592 (143)¶
Ischaemia					
5 min	–647 (153)	–427 (72)	–754 (21)	–989 (198)	–845 (47)
20 min	–641 (146)	–450 (69)	–758 (27)	–1028 (209)	–859 (59)
30 min	–664 (154)	–463 (67)	–769 (24)	–1023 (200)	–848 (49)
44 min	–682 (147)	–465 (71)	–790 (22)	–1048 (191)	–849 (44)
Reperfusion					
5 min	–993 (159)	–705 (119)	–926 (82)	–1737 (292)*	–1348 (137)
15 min	–1030 (156)	–845 (101)	–931 (85)	–1882 (322)†	–1552 (170)
30 min	–1000 (149)	–896 (147)	–1384 (144)	–2057 (348)†	–2150 (208)‡
60 min	–1002 (172)	–876 (129)	–1301 (143)	–1905 (300)†	–2046 (176)‡
90 min	–906 (175)	–798 (118)	–1255 (125)	–1841 (293)†	–1704 (215)*

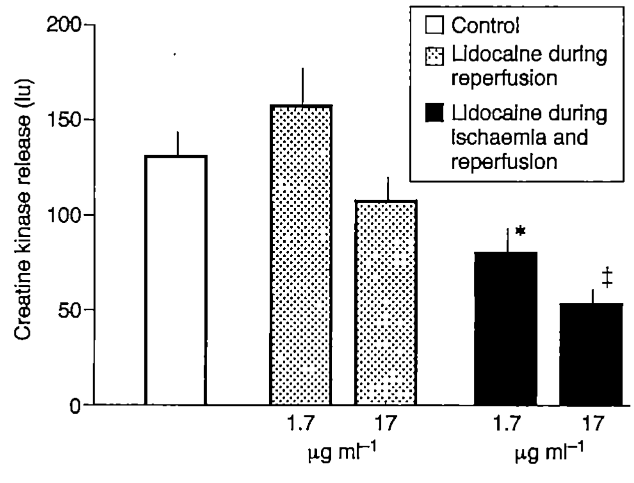

Fig 3 Cumulative creatine kinase release in the five groups. Lidocaine administered during ischaemia and early reperfusion reduced creatine kinase release. Lidocaine administration during reperfusion only had no effect on this marker of cellular damage. Data are mean (SEM). *P=0.042, ‡P=0.001 *vs* control. n=10 in control group; n=11 in all other groups.

through sodium channels is an important route of hypoxic sodium loading,[7 23] and blockade of these channels by lidocaine can reduce and delay ischaemic sodium accumulation.[4 5] This may result in protection via two pathways. First, lidocaine leads to adenosine triphosphate preservation, probably as a consequence of a reduced activity of the energy-consuming Na^+/K^+-ATPase because of impaired sodium loading.[4] Second, the increase in $[Na^+]_i$ is known to be closely connected to an increase in intracellular calcium via Na^+/Ca^{2+} exchange.[24] It has also been shown that lidocaine reduces ischaemic calcium loading.[6 7] Calcium overload is thought to be a major factor in reperfusion injury,[25] and lidocaine may reduce calcium overload by attenuating intracellular sodium overload.

Lidocaine as a calcium channel blocker

Calcium channel blockers are known to reduce ischaemic injury and myocardial reperfusion injury.[26 27] There is evidence that lidocaine acts as a calcium channel blocker,[10 11] and this may be another way in which it reduces calcium overload.

Protection of the cellular membrane

Destruction of the cellular membrane by reactive compounds generated during ischaemia and reperfusion is another important factor in ischaemia–reperfusion injury. Long-chain acylcarnitines participate in the production of ischaemia–reperfusion injury.[28 29] Oxygen free radicals generated particularly during the first few minutes of reperfusion play an important role in the development of reperfusion injury by attacking fatty acids, which lead to lipid peroxidation of the cellular membrane.[2 30] Lidocaine protects myocardium from long-chain acylcarnitine-induced mechanical and metabolic derangement,[8] and is a powerful antioxidant which can scavenge oxygen free radicals.[9]

Negative inotropic effect of lidocaine

Negative inotropy may reduce myocardial oxygen consumption and, thereby, ischaemic injury. In addition, a complete or a partial contractile blockade at the onset of reperfusion can also reduce reperfusion injury.[31 32] These effects may only be relevant at higher concentrations of lidocaine at which it has negative inotropic effects.[33]

Calcium overload and the destruction of cellular membrane by reactive oxygen species play a role in the development not only of ischaemic injury but also of myocardial reperfusion injury. Together with the known effects of lidocaine, these findings indicate that the cardioprotection produced by lidocaine may at least in part be caused by an effect on myocardial reperfusion injury.

In all studies showing cardioprotection by lidocaine against ischaemia–reperfusion injury, lidocaine was administered in a manner that did not allow effects on ischaemic injury to be distinguished from effects on reperfusion injury.[12–22] Therefore, it is unclear if late administration of lidocaine at the beginning of reperfusion can still be protective.

In the present study, lidocaine was administered at two concentrations during ischaemia and maintained during early reperfusion. In these two groups, functional recovery during reperfusion was improved (LVDP, dP/dt_{max}) accompanied by a smaller contracture (LVEDP) and a higher myocardial oxygen consumption, indicating a greater amount of viable myocardial tissue. CK release as a variable of cellular damage was reduced. These results demonstrate that lidocaine protects the myocardium from ischaemia–reperfusion injury in our model. The question of whether reduction of reperfusion injury contributes to this protective effect can be answered by looking at the two groups of our study which received lidocaine only during early reperfusion. While lidocaine administration during ischaemia *and* reperfusion was clearly cardioprotective, no protection was observed when lidocaine was given only during reperfusion: there was no improvement of functional recovery (LVDP, dP/dt_{max}), myocardial oxygen consumption was similar to that in the control group, myocardial contracture (LVEDP) was unchanged, and no reduction in cellular damage was detected (as assessed by CK release). In the group that received lidocaine at the higher concentration during reperfusion, there was a tendency to better functional recovery, lower contracture and reduced CK release. This effect was not statistically significant and occurred at a very high lidocaine concentration. However, if there is an effect of lidocaine at this high concentration on myocardial reperfusion injury, this effect is very small and of little clinical relevance.

Our study shows that lidocaine protects the isolated rat heart in an ischaemia–reperfusion situation, but reduction of reperfusion injury does not contribute to this protective effect. While lidocaine given during ischaemia with the resulting reduction in $[Na^+]_i$ probably protected myocardium from ischaemic injury, the antioxidant effect of lidocaine, and its effect on intracellular calcium concentration—either indirect (by reduction of Na^+/Ca^{2+} exchange) or direct (by its possible calcium channel blocking properties)—were not sufficient to protect the hearts against reperfusion injury.

Critique of methods

We used lidocaine at concentrations of 1.7 and 17 $\mu g\ ml^{-1}$. Therapeutic plasma concentrations of lidocaine are approximately 1.5–5 mg l^{-1}, while 60–80% of lidocaine is protein bound.[34] Therefore, the therapeutic free plasma concentration of lidocaine is not higher than 2 $\mu g\ ml^{-1}$ (range: 0.3–2 $\mu g\ ml^{-1}$); 1.7 $\mu g\ ml^{-1}$ lidocaine thus corresponds to high clinically achievable plasma concentrations, while the higher concentration of 17 $\mu g\ ml^{-1}$ is in the clinically toxic range. It could be argued that plasma-bound lidocaine in a blood-perfused model could still exert its antioxidant properties, but having studied a concentration of 17 $\mu g\ ml^{-1}$, we can now exclude the possibility that this could have had an effect on reperfusion injury.

Lidocaine reduces neutrophil adherence *in vitro*[35] and *in vivo*.[36] It also reduces lysosomal enzyme release and superoxide anion production by these inflammatory cells.[37] A role for infiltrating leucocytes has been proposed in the development of reperfusion injury.[38] As we used cell-free saline perfusion, an effect of lidocaine on reperfusion injury in a blood-perfused heart cannot be completely excluded.

In summary, we found that lidocaine at a clinically relevant concentration (and a 10-fold higher concentration) protects the myocardium from ischaemic injury, but not from myocardial reperfusion injury. The known cardioprotective effects of lidocaine in ischaemia–reperfusion situations appear to be a consequence of anti-ischaemic properties only and not of reduction in myocardial reperfusion injury. Therefore, we suggest that post-ischaemic lidocaine treatment does not seem to be advantageous in terms of reduction of myocardial necrosis and improvement of recovery after ischaemia.

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References

1 Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. *J Am Coll Cardiol* 1983; **1**: 1235–46

2 Simpson PJ, Mickelson JK, Lucchesi BR. Free radical scavengers in myocardial ischemia. *Fed Proc* 1987; **46**: 2413–21

3 Schlack W, Hollmann M, Stunneck J, Thämer V. Effect of halothane on myocardial reoxygenation injury in the isolated rat heart. *Br J Anaesth* 1996; **76**: 860–7

4 Butwell NB, Ramasamy R, Lazar I, Sherry AD, Malloy CR. Effect of lidocaine on contracture, intracellular sodium and pH in ischemic rat hearts. *Am J Physiol* 1993; **264**: H1884–9

5 Tani M, Neely JR. Role of intracellular Na^+ in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H^+–Na^+ exchange. *Circ Res* 1989; **65**: 1045–56

6 Pike MM, Kitakaze M, Chacko VP, Marban E. Lidocaine prevents the increase in myocardial free calcium during ischemia and reperfusion: an antiarrhythmic mechanism? *Circulation* 1987; **76**: IV-16[Abstract]

7 Haigney MC, Lakatta EG, Stern MD, Silverman HS. Sodium channel blockade reduces hypoxic sodium loading and sodium-dependent calcium loading. *Circulation* 1994; **90**: 391–9

8 Arakawa J, Hara A, Kokita N. Lidocaine attenuates mechanical and metabolic derangements induced by palmitoyl-L-carnitine in the isolated perfused rat heart. *Pharmacology* 1997; **55**: 259–68

9 Das DK, Misra HP. Lidocaine: a hydroxyl radical scavenger and singlet oxygen quencher. *Mol Cell Biochem* 1992; **115**: 179–85

10 Josephson IR. Lidocaine blocks Na, Ca and K currents of chick ventricular myocytes. *J Mol Cell Cardiol* 1988; **20**: 593–604

11 Sugiyama K, Muteki T. Local anesthetics depress the calcium current of rat sensory neurons in culture. *Anesthesiology* 1994; **80**: 1369–78

12 Kojima M, Miura M. Protective effect of lidocaine on the ischemic-reperfused rat heart: a phosphorus 31 nuclear magnetic resonance study. *Basic Res Cardiol* 1993; **28**: 619–28

13 Latocha G, Bernauer W. Effect of antiarrhythmic drugs on the postischaemic metabolic recovery of isolated rat hearts. *Arch Int Pharmacodyn* 1991; **312**: 39–54

14 Ohmura T, Muramatsu I, Kigoshi S, *et al.* Novel cardioprotective effects of TYB-3823 on ischemic damage in the working hearts of rats: comparison with lidocaine. *J Pharmacol Exp Ther* 1990; **254**: 696–701

15 Vitola JV, Forman MB, Holsinger JP, Atkinson JB, Murray JJ. Reduction of myocardial infarct size in rabbits and inhibition of activation of rabbit and human neutrophils by lidocaine. *Am Heart J* 1997; **133**: 315–22

16 Wendland MF, Saeed M, Kondo C, Derugin N, Higgins CB. Effect of lidocaine on acute regional myocardial ischemia and reperfusion in the cat. An in-vivo ^{31}P magnetic resonance spectroscopy study. *Invest Radiol* 1993; **28**: 619–28

17 Hatori N, Roberts RL, Tadokoro H, *et al.* Differences in infarct size with lidocaine as compared with bretylium tosylate in acute myocardial ischemia and reperfusion in pigs. *J Cardiovasc Pharmacol* 1991; **18**: 581–8

18 Lee R, Nitta T, Schmid RA, Schuessler RB, Harris KM, Gay WA. Retrograde infusion of lidocaine or L-arginine before reperfusion reduces myocardial infarct size. *Ann Thorac Surg* 1998; **65**: 1353–9

19 Lesnefsky EJ, Van Benthuysen KM, McMurtry IF, Shikes RH, Johnston RB, Horwitz LD. Lidocaine reduces canine infarct size and decreases release of a lipid peroxidation product. *J Cardiovasc Pharmacol* 1989; **13**: 895–901

20 Nasser FN, Walls JT, Edwards WD, Harrison CE. Lidocaine-induced reduction in size of experimental myocardial infarction. *Am J Cardiol* 1980; **46**: 967–75

21 Okamura T, Sunamori M, Suzuki A. Protective effect of lidocaine in reperfused ischemic myocardium. *Jpn Circ J* 1982; **46**: 657–62

22 Schaub RG, Stewart G, Strong M, Ruotolo R, Lemole G. Reduction of ischemic myocardial damage in the dog by lidocaine infusion. *Am J Pathol* 1977; **87**: 399–414

23 Pike MM, Kitakaze M, Marban E. Increase in intracellular free sodium concentration during ischemia revealed by ^{23}Na NMR in perfused ferret hearts. *Circulation* 1988; **78**: II-151 [Abstract]

24 Tani M, Neely JR. Na^{+} accumulation increases Ca^{2+} overload and impairs function in anoxic rat heart. *J Mol Cell Cardiol* 1990; **22**: 57–72

25 Siegmund B, Schlüter KD, Piper HM. Calcium and the oxygen paradox. *Cardiovasc Res* 1993; **27**: 1778–83

26 Nayler WG. Basic mechanisms involved in the protection of the ischaemic myocardium. The role of calcium antagonists. *Drugs* 1991; **42**: 21–7

27 Herzog WR, Vogel RA, Schlossberg ML, Edenbaum LR, Scott HJ, Serebruany VL. Short-term low dose intracoronary diltiazem administered at the onset of reperfusion reduces myocardial infarct size. *Int J Cardiol* 1997; **59**: 21–7

28 Corr PB, Saffitz JE, Sobel BE. Lysophospholipids, long chain acylcarnitines and membrane dysfunction in the ischemic heart. *Basic Res Cardiol* 1987; **82**: 199–208

29 Corr PB, Creer MH, Yamada KA, Saffitz JE, Sobel BE. Prophylaxis of early ventricular fibrillation by inhibition of acylcarnitine accumulation. *J Clin Invest* 1989; **83**: 927–36

30 Kloner RA, Przyklenk K, Whittaker P. Deleterious effects of oxygen radicals in ischemia/reperfusion. Resolved and unresolved issues. *Circulation* 1989; **80**: 1115–27

31 Schlack W, Uebing A, Schäfer M, *et al.* Regional contractile blockade at the onset of reperfusion reduces infarct size in the dog heart. *Pflügers Arch Eur J Physiol* 1994; **428**: 134–41

32 Schlack W, Uebing A, Schäfer M, *et al.* Intracoronary SIN-1C during reperfusion reduces infarct size in dog. *J Cardiovasc Pharmacol* 1995; **25**: 424–31

33 Lynch C. Depression of myocardial contractility *in vivo* by bupivacaine, etidocaine, and lidocaine. *Anesth Analg* 1986; **65**: 551–9

34 Scott DK. Cardiac arrhythmias. In: Walker R, Edwards C, eds. *Clinical Pharmacy and Therapeutics*. New York: Churchill Livingstone, 1994; 281–91

35 Schiffer CA, Sanel FT, Young VB, Aisner J. Reversal of granulocyte adherence to nylon fibers using local anesthetic agents: possible application to filtration leukapheresis. *Blood* 1977; **50**: 213–25

36 MacGregor RR, Thorner RE, Wright DM. Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 1980; **56**: 203–9

37 Peck SL, Johnston RB, Horwitz LD. Reduced neutrophil superoxide anion release after prolonged infusions of lidocaine. *J Pharmacol Exp Ther* 1985; **235**: 418–22

38 Litt MR, Jeremy RW, Weisman HF, Winkelstein JA, Becker LC. Neutrophil depletion limited to reperfusion reduces myocardial infarct size after 90 minutes of ischemia. Evidence for neutrophil-mediated reperfusion injury. *Circulation* 1989; **80**: 1816–27

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Propofol inhibits FMLP-stimulated phosphorylation of p42 mitogen-activated protein kinase and chemotaxis in human neutrophils

T. Nagata*, M. Kansha, K. Irita and S. Takahashi

Department of Anesthesiology and Critical Care Medicine, Kyushu University, Fukuoka, Japan
**Corresponding author: 3-1-1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan*

Propofol is used in the peri-operative setting and may affect some neutrophil functions. The effects of propofol on the function and intracellular signal transduction systems of neutrophils is controversial. Mitogen-activated protein kinase families (MAPKs) are members of the intracellular signal-transducing systems in eukaryotes. MAPKs have been shown to be involved in neutrophil chemotaxis by the use of PD98059, the specific inhibitor of MAPK/ERK kinase (MEK). The effects of propofol in dimethyl sulfoxide on phosphorylation of MAPKs and chemotaxis were investigated in human neutrophils. Isolated neutrophils (2×10^7 cells per ml) from healthy volunteers were incubated with propofol (2–500 µM) and stimulated by *N*-formyl-L-methionyl-phenylalanine (FMLP) (100 nM). The effects of propofol on the phosphorylation of p44/42 MAPK were investigated by immunoblotting. The effects of FMLP (1 µM) on chemotaxis were investigated with the under-agarose method. The phosphorylation of p42 MAPK and chemotaxis stimulated by FMLP were both inhibited by propofol at clinically relevant concentrations (≥10 and ≥20 µM respectively). PD98059 (50 µM) also inhibited chemotaxis stimulated by FMLP, suggesting the involvement of p42 MAPK in the response. Propofol might therefore inhibit human neutrophil chemotaxis, at least in part, by suppressing the p44/42 MAPK pathway.

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Neutrophils play an important role in the peri-operative period. In response to inflammatory stimuli, neutrophils exit the microvasculature, move along chemoattractant gradients and ingest and kill invading pathogens. Such microbicidal activity has been established to be an essential component of the host defence system.[1] Furthermore, there is increasing evidence that neutrophils play an important role in the pathogenesis of ischaemia/reperfusion injury as well as in systemic inflammatory response syndrome.[2] Therefore, controlling neutrophil function during the peri-operative period appears to be an important component of anaesthesia.[3]

Propofol has been widely used in the induction and maintenance of anaesthesia and the sedation of patients in intensive care units. Accordingly, it is important to determine the effects of this agent on the immune system. It has been reported in an *in vitro* study that propofol inhibits such neutrophil functions as polarization,[4] chemotaxis,[5–7] phagocytosis,[7 8] respiratory burst[9 10] and bactericidal activity[6] at clinically achievable concentrations. However, the degree of these inhibitory effects varies considerably. Furthermore, some studies have failed to observe an inhibitory effect of propofol on neutrophil function.[6 7 11] Therefore, the effects of propofol on neutrophils remain unclear. Moreover, there have been few mechanistic studies.[7]

Mitogen-activated protein kinases (MAPKs) are members of the serine/threonine protein kinase family, and mediate signal transduction from the cell surface to the nucleus. They are highly conserved in many types of eukaryotes from yeast to mammalian cells, including human neutrophils, suggesting that the signalling cascade involving MAPKs may be very important in signal transduction in eukaryotes.[12 13] Recently, three mammalian MAPKs have been identified,[14] including extracellular signal-regulated kinase (ERKs or p44/42 MAPK), c-Jun *N*-terminal kinase (JNK) and p38 MAPK. MEK (MAPK/ERK kinase) is the specific kinase of p44/42 MAPK and the phosphorylated

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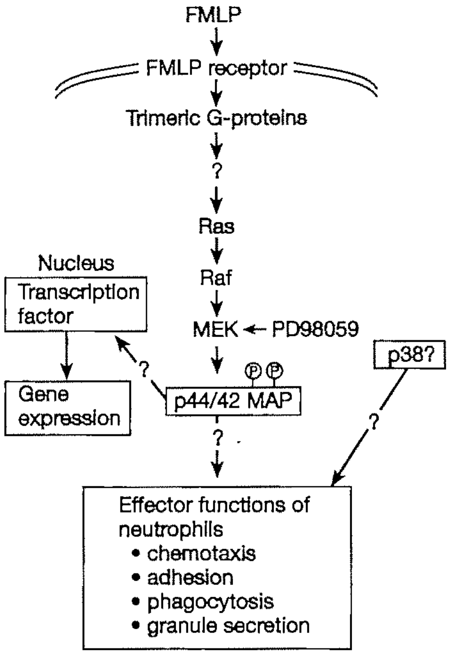

Fig 1 Possible signal transduction pathway via MAPK in neutrophils. The binding of FMLP to its receptor on the plasma membrane activates the Ras–Raf–MEK–p44/42 MAPK pathway through heterotrimeric GTP binding proteins. MEK is a specific activator of p44/42 MAPK. PD98059 selectively inhibits MEK. This signalling cascade is considered to participate in the activation of various functions of neutrophils. The participation of other MAPK families, such as p38, has been reported recently. In various cells, the activated p44/42 MAPK activates transcription factors by protein phosphorylation, and thus leads to gene expression.

form of p44/42 MAPK is active.[15] MEK is directly activated by Raf-1 kinase and Raf-1 kinase is modulated by Ras. In human neutrophils, p44/42 MAPK has been reported to be activated rapidly in response to various stimuli, including chemotactic factors,[16] while p44/42 MAPK has been reported to participate in various neutrophil functions, such as chemotaxis,[17] [18] adhesion, phagocytosis, granule secretion and respiratory burst. *N*-Formyl-L-methionyl-phenylalanine (FMLP), a chemoattractant, activates the Ras–Raf–MEK–p44/42 MAPK pathway[19] through the FMLP receptor activating the trimeric GTP-binding protein (Fig. 1). Downstream activity of p44/42 MAPK in the intracellular signal transduction pathway has not been elucidated.

In this study, we used human neutrophils to examine the effects of propofol on the phosphorylation of p44/42 MAPK and chemotaxis in response to the chemotactic peptide FMLP.

Materials and methods

Materials

FMLP, cytochalasin B, chymostatin, ethylenediamine tetraacetate (EDTA), leupeptin, Nonidet P-40 (Np-40), 2-mercaptoethanol, catalase and agarose (type II) were obtained from Sigma (St Louis, MO, USA). Bromochloroidolyl phosphate (BPB), (*p*-amidinophenyl) methanesulphonyl fluoride (APMSF) and HEPES were from Wako Pure Chemical Industries (Osaka, Japan). Pepstatin and sodium orthovanadate (Na_3VO_4) were from Nacalai Tesque (Kyoto, Japan). Propofol was from RBI (Natick, MA, USA). Superoxide dismutase (SOD) was from Toyobo (Osaka, Japan). Phospho-p44/42 MAP kinase antibody and PD98059 were from New England Biolabs (Beverly, MA, USA). Anti-ERK1 antibody was from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Enhanced chemiluminescence (ECL®) Western blotting detection reagents and antibody were obtained from Amersham International (Amersham, UK). Ficoll was from Pharmacia Biotech (Uppsala, Sweden). Conray (sodium iothalamate 60.8% w/v) was from Daiichi Pharmaceutical (Tokyo, Japan). HEPES-buffered saline (HBS), used for phosphorylation of p44/42 MAPK, contained 135 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 0.6 mM $CaCl_2$, 2 mM glucose and 20 mM HEPES (pH 7.4 at 37°C). Radio-immunoprecipitation (RIPA) buffer contained 1 mM EDTA, 150 mM NaCl, 10 mM Tris, 1% Np-40, 0.1% sodium deoxycholate and 0.1% sodium dodecyl sulphate (SDS) (pH 7.4 at 25°C). Just before cell lysis, RIPA buffer was added containing 10 mM sodium fluoride, 25 μM APMSF, 40 μM leupeptin, 50 μM chymostatin, 1.5 mM pepstatin and 1 mM Na_3VO_4 as protease inhibitors. Laemmli buffer contained 62.5 mM Tris, 2% SDS, 10% glycerol, 0.002% BPB, and 5% 2-mercaptoethanol (pH 6.8, 25°C). Medium 199 (with Earle's salts and L-glutamine without sodium bicarbonate) and fetal bovine serum (FBS) were from Life Technologies (Grand Island, NY, USA). Medium 199 was used in the chemotaxis assay as the Minimum Essential Medium (MEM). MEM was buffered with $NaHCO_3$ to pH 7.4 at 37°C and was then sterilized by membrane filtration. Just before use in agarose plates, MEM was added containing 10% FBS and 0.5% agarose. FMLP, cytochalasin B, chymostatin, pepstatin, PD98059 and propofol were dissolved in dimethyl sulfoxide (DMSO).

Isolation of neutrophils

Neutrophils were isolated from healthy human volunteers. The majority of erythrocytes in heparinized whole blood were removed by dextran sedimentation at room temperature. The sample was then cooled to 4°C to prevent neutrophil activation. The remaining erythrocytes were eliminated by hypotonic lysis. Monocytes and lymphocytes were removed by Conray–Ficoll centrifugation.[20] The isolated neutrophils were washed twice with 0.9% sodium chloride and suspended in HBS or MEM. Cell viability after incubation with drugs was estimated using a trypan blue dye exclusion test.

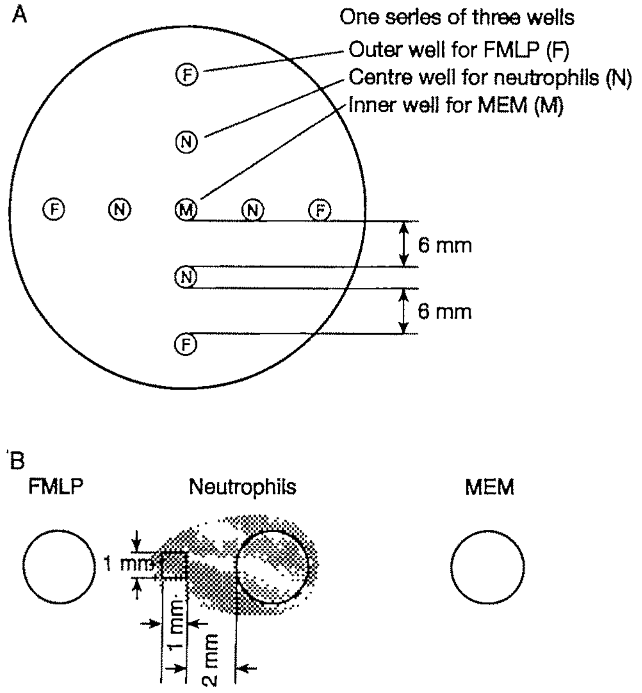

Fig 2 (A) Schematic representation of the under-agarose method. Four series of three wells, measuring 3 mm in diameter and spaced 6 mm apart, were cut into 60×15 mm agarose plates. The centre well received 10 μl of the prepared cell suspension. The outer wells received 10 μl FMLP dissolved in MEM and the inner wells received 10 μl MEM. (B) Chemotaxis pattern of neutrophils. The number of neutrophils was counted in 1×1 mm square areas, which were 2 mm from the edges of the neutrophil wells.

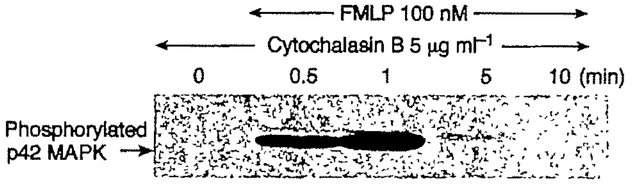

Fig 3 Time course of phosphorylation of p44/42 MAPK of human neutrophils. The cells were stimulated with 5 μg ml^{-1} cytochalasin B and 100 nM FMLP, as described in Materials and methods. The arrow indicates the bands of phosphorylated p42 MAPK. The band of phosphorylated p44 MAPK is not shown in this blot. Phosphorylation of p42 MAPK reached a maximum 1 min after FMLP stimulation.

Phosphorylation of MAPKs

Neutrophils, suspended in HBS at 2×10^7 cells per ml, were incubated for 30 s with propofol or DMSO. The final concentration of DMSO in all sample was 3%. Propofol was prepared at final concentrations of 2–500 μM. After pretreatment with propofol, cells were stimulated with cytochalasin B (5 μg ml^{-1}) for 5 min followed by FMLP (100 nM) for 1 min at 37°C. The reaction was terminated by adding cold 0.9% NaCl. The cells were immediately lysed in RIPA buffer at 4°C and then centrifuged (10 min, 4°C, 13 000 *g*), and the cell lysates were analysed by immunoblotting. All samples were diluted with Laemmli buffer and boiled for 5 min before separation by SDS/10% polyacrylamide gel electrophoresis. Proteins within the gel were transferred to nitrocellulose membranes and immunoblotted with phospho-p44/42 MAP kinase antibody or anti-ERK1 antibody. Phospho-p44/42 MAP kinase antibody produced by immunizing rabbits with synthetic peptide corresponding to human p44 MAPK detects phosphorylation of both p44 and p42 MAPK, and anti-ERK1 antibody detects both p44 and p42 MAPK. Antibody binding was detected by ECL. Visualized bands on films were captured and stored as images on a computer using a scanner (Opal Ultra; Druckmaschina, Heidelberg, Germany), and analysed with NIH Image (version 1.61), a public domain image analysis program from the National Institutes of Health (Bethesda, MD, USA), as the densitometric analyser.

Chemotaxis

Neutrophils suspended in MEM at 1×10^7 cells per ml were incubated at 37°C for 30 min with propofol, 50 μM PD98059 (specific inhibitor of MEK) or 0.1% DMSO. Propofol concentrations ranged from 10 to 200 μM. To prepare the agarose plates for the under-agarose method,[21] 5 ml of agarose medium was added to each 60×15 mm dish. Four series of three wells, 3 mm in diameter and spaced 6 mm apart, were cut in each plate (Fig. 2A). Each well received 10 μl of solution. Neutrophils (1×10^5 cells) incubated with the reagents mentioned above were added to the centre well of each three-well series. The outer and inner wells received MEM with or without 1 μM FMLP (the final concentration of DMSO was 0.1%). Plates were then incubated at 37°C in 5% carbon dioxide for 3 h. After incubation, the neutrophils were fixed by addition of 5 ml absolute methanol overnight and the gels were then hardened by addition of 3 ml 47% formalin for 30 min. After fixation, the gels were gently removed and the neutrophils that were fixed on the dishes were stained with Giemsa stain. Micrographs (×40) of the cell migration patterns were taken, scanned and stored on a computer. The number of neutrophils in a square area (1×1 mm) 2 mm from the edge of the centre well, towards the outer well, was counted using the particle-counter function of NIH Image (Fig. 2B).

Statistical analysis

All data were analysed by the Mann–Whitney test and are presented as mean (SEM). Differences were considered to be significant when $P<0.01$.

Results

Effects of propofol on FMLP-induced phosphorylation of p44/42 MAPK

Initially, we examined the effect of FMLP with cytochalasin B, which primes neutrophils, thus enhancing

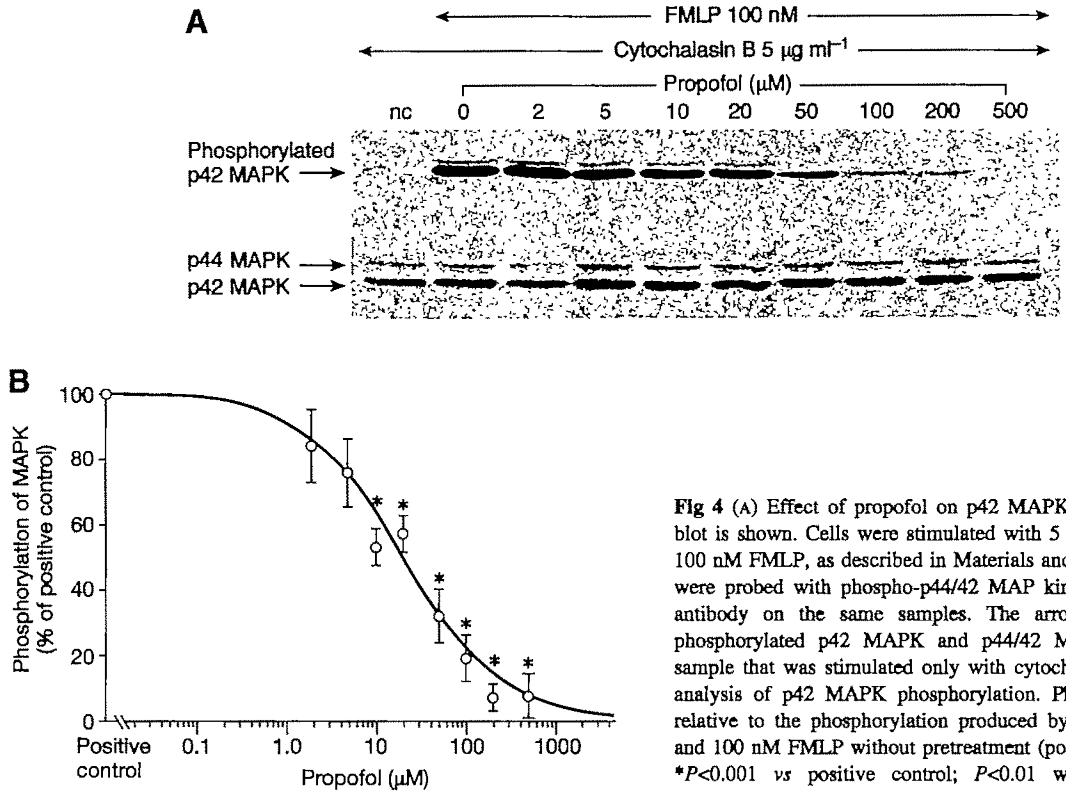

Fig 4 (A) Effect of propofol on p42 MAPK phosphorylation. A typical blot is shown. Cells were stimulated with 5 μg ml^{-1} cytochalasin B and 100 nM FMLP, as described in Materials and methods. The protein blots were probed with phospho-p44/42 MAP kinase antibody or anti-ERK1 antibody on the same samples. The arrows indicate the bands of phosphorylated p42 MAPK and p44/42 MAPK. nc=negative control sample that was stimulated only with cytochalasin B. (B) Densitometric analysis of p42 MAPK phosphorylation. Phosphorylation is expressed relative to the phosphorylation produced by 5 μg ml^{-1} cytochalasin B and 100 nM FMLP without pretreatment (positive control). Means (SEM) *P<0.001 *vs* positive control; P<0.01 was considered to indicate significance. Negative control, FMLP 0 μM.

the response to chemoattractants, on the phosphorylation of p44/42 MAPK. As shown in Fig. 3, only p42 MAPK was phosphorylated. In an analysis of the molecular weight, upper thin bands were observed as part of the phosphorylated p42 MAPK. As there were more phosphorylated residues than in the lower bands of phosphorylated p42 MAPK, the molecular weight of MAPK in these thin bands was thought to be a little higher. As shown in the lower blot of Fig.4A, the bands of p42 MAPK were thicker than the bands of p44 MAPK, indicating that the amount of p42 MAPK was greater than that of p44 MAPK. p42 MAPK has also been reported to be predominant in human neutrophils.[22]

Phosphorylation of p42 MAPK in human neutrophils activated by 100 nM FMLP reached a maximum at 1 min and disappeared within 5 min. Accordingly, the FMLP stimulation time for the phosphorylation of MAPKs was set at 1 min in the subsequent experiments (Fig. 3).

FMLP-stimulated phosphorylation of p42 MAPK was inhibited by propofol at concentrations above 10 μM (n=6), whereas the quantity of p42 MAPK was not affected. The 50% inhibitory concentration (IC_{50}) for the inhibition of p42 MAPK phosphorylation by propofol was 20 (12) μM. The inhibitory effect of propofol on p42 MAPK phosphorylation seemed to be concentration-dependent, and was observed at clinically achievable concentrations (Fig. 4A and B).

Phosphorylation of p42 MAPK induced by FMLP was also observed in the presence of 100 μg ml^{-1} SOD or 40 μg ml^{-1} catalase, indicating that phosphorylation is not secondary to the production of superoxide and hydrogen peroxide (results not shown).

Effects of propofol on FMLP-induced chemotaxis

As shown in Fig. 5, propofol inhibited FMLP-stimulated chemotaxis of neutrophils at concentrations above 20 μM (n=12) in a concentration-dependent manner. The IC_{50} for the inhibition of neutrophil chemotaxis by propofol was 88.0 (2.5) μM. PD98059 (50 μM) also inhibited the chemotaxis of neutrophils, indicating that the p44/42 MAPK pathway is involved in regulating the chemotaxis of neutrophils. These concentrations of propofol were clinically achievable, and were identical with the concentrations required to inhibit the phosphorylation of p42 MAPK induced by FMLP.

Discussion

There have been various reports of the inhibitory effects of propofol on neutrophil activity. Various concentrations of propofol, ranging from 11 to 280 μM, were reported to be effective in these studies. In most of these reports, propofol inhibited neutrophil activity at a clinically achievable concentration, which has been reported to be approximately 30 μM (5 μg ml^{-1}) for surgical anaesthesia and 15 μM (3 μg ml^{-1}) for sedation. It is important to rule out the effect of the solvent of propofol (10% Intralipid), as Heine and colleagues[23] reported that the inhibitory effect on respira-

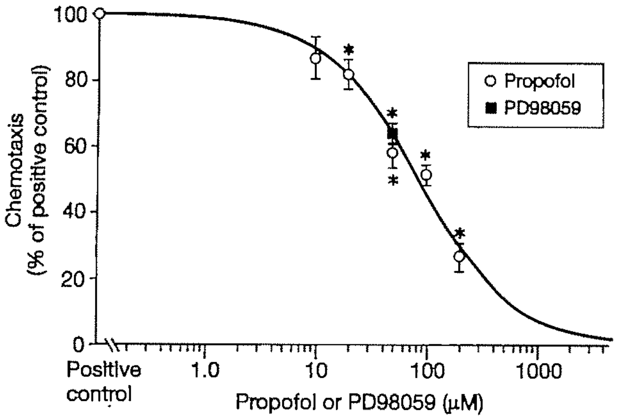

Fig 5 Effect of propofol and PD98059 on neutrophil chemotaxis. The under-agarose method was used to study chemotaxis as described in Materials and methods. Chemotaxis is expressed as the percentage of chemotaxis caused by 1 μM FMLP without pretreatment (positive control). Mean (SEM); *$P<0.0001$ *vs* positive control; $P<0.01$ was considered to indicate significance.

tory burst was caused by the solvent. Intralipid affects neutrophil activity in a concentration-dependent manner.[24] In our study, we used propofol dissolved in DMSO to examine the effect of pure propofol on neutrophil activity. Although the IC_{50} value required for propofol to inhibit the chemotaxis [88.0 (2.5) μM] exceeded those seen clinically, we did demonstrate that propofol significantly inhibited chemotaxis at clinically achievable concentrations (⩾20 μM). Direct inhibitory effects of propofol on respiratory burst,[9] polarization,[4] phagocytosis[8] and chemotaxis[6] have also been reported.

We have also shown that propofol at clinically achievable concentrations (⩾10 μM) inhibited the phosphorylation of p42 MAPK. Although some investigators have reported the relationship of neutrophil activity with the p44/42 MAPK pathway, this subject remains controversial. Kuroki and O'Flaherty[17] reported that PD98059, a specific inhibitor of MEK, inhibited FMLP-induced chemotaxis of neutrophils. Hii *et al.*[18] observed partial inhibition of chemotaxis and marked inhibition of chemokinesis by PD98059. These inhibitory effects of PD98059 on neutrophil chemotaxis suggest the involvement of the p44/42 MAPK pathway. However, in their studies, after almost completely inhibiting phosphorylation and the activity of p44/42 MAPK, PD98059 (50 μM) only partially inhibited chemotaxis. In our studies, the inhibitory effect of PD98059 (50 μM) on chemotaxis was also partial. These results suggest multiple pathways in FMLP-induced chemotaxis. On the other hand, Zu *et al.*[25] reported that PD98059 did not inhibit FMLP-induced chemotaxis. These authors suggested the involvement of p38 MAPK in FMLP-induced chemotaxis of neutrophils, because the specific inhibitors of p38 MAPK (SB20358) inhibited chemotaxis.[25] Furthermore, Coffer *et al.*[26] reported the possibility that p38 MAPK participates in neutrophil chemotaxis. They also reported that PD98059 did not inhibit FMLP-induced chemotaxis. This discrepancy may be explained partly by methodological differences. Kuroki and O'Flaherty[17] and Hii *et al.*[18] used the same agarose method as in the present study, whereas Zu *et al.*[25] and Coffer *et al.*[26] used the filter method. The agarose method may be more sensitive than a filter method in evaluating cell adhesion, as neutrophils should adhere horizontally to the plate for migration.[27] MAPK is also known as microtubule-associated protein kinase. An association of p44/42 MAPK with cytoskeletal alteration has also been observed, for example, in NIH 3T3 mouse fibroblasts.[28] In addition, propofol was found to inhibit the polarization of neutrophils,[4] which is an expression of cytoskeletal alteration and is essential for chemotaxis.

Although p44/42 MAPK has been reported to activate transcription factors in neutrophils,[29] it is not known how these transcription factors are involved in neutrophil activity. Because some neutrophil responses to stimuli such as chemotaxis are induced immediately, the signal transmitted by activated p44/42 MAPK does not necessarily induce gene expression.

In conclusion, our observations indicate the possibility that some of the inhibitory effects of propofol on neutrophil activity may be mediated by inhibition of the p44/42 MAPK pathway. The clinical significance of propofol-induced inhibition of neutrophil activity, however, is not clear. Whether such an inhibition is beneficial or detrimental should also be evaluated in a clinical setting. For example, tourniquet-induced ischaemia/reperfusion injury has been shown to be lessened by the administration of propofol in orthopaedic patients.[30]

References

1 Minakami S, Kakinuma K, Takeshige K. *Leukocytes and Biological Defence*. Tokyo: Kodansha, 1990

2 Partrick DA, Moore FA, Moore EE, Barnett CC Jr, Silliman CC. Neutrophil priming and activation in the pathogenesis of postinjury multiple organ failure. *New Horizons* 1996; **4**: 194–210

3 McBride WT, Armstrong MA, McBride SJ. Immunomodulation: an important concept in modern anaesthesia. *Anaesthesia* 1996; **51**: 465–73

4 O'Donnell NG, McSharry CP, Wilkinson PC, Asbury AJ. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin. *Br J Anaesth* 1992; **69**: 70–4

5 Jensen AG, Dahlgren C, Eintrei C. Propofol decreases random and chemotactic stimulated locomotion of human neutrophils *in vitro*. *Br J Anaesth* 1993; **70**: 99–100

6 Skoutelis A, Lianou P, Papageorgiou E, *et al.* Effects of propofol and thiopentone on polymorphonuclear leukocyte functions *in vitro*. *Acta Anaesthesiol Scand* 1994; **38**: 858–62

7 Mikawa K, Akamatsu H, Nishina K, *et al.* Propofol inhibits human neutrophil functions. *Anesth Analg* 1998; **87**: 695–700

8 Krumholz W, Endrass J, Hempelmann G. Propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli* by polymorphonuclear leukocytes *in vitro*. *Can J Anaesth* 1994; **41**: 446–9

9 Murphy PG, Ogilvy AJ, Whiteley SM. The effect of propofol on

the neutrophil respiratory burst. *Eur J Anaesthesiol* 1996; **13**: 471–3

10 Heine J, Jaeger K, Osthaus A *et al.* Anaesthesia with propofol decreases FMLP-induced neutrophil respiratory burst but not phagocytosis compared with isoflurane. *Br J Anaesth* 2000; **85**: 424–430

11 Davidson JA, Boom SJ, Pearsall FJ, Zhang P, Ramsay G. Comparison of the effects of four i.v. anaesthetic agents on polymorphonuclear leucocyte function. *Br J Anaesth* 1995; **74**: 315–8

12 Seger R, Krebs EG. The MAPK signaling cascade. *FASEB J* 1995; **9**: 726–35

13 Kansha M, Nagata T, Irita K, Takahashi S. Dibucaine and tetracaine inhibit the activation of mitogen-activated protein kinase mediated by L-type calcium channels in PC12 cells. *Anesthesiology* 1999; **91**: 1798–1806

14 Cano E, Mahadevan LC. Parallel signal processing among mammalian MAPKs. *Trends Biochem Sci* 1995; **20**: 117–22

15 Anderson NG, Maller JL, Tonks NK, Sturgill TW. Requirement for integration of signals from two distinct phosphorylation pathways for activation of MAP kinase. *Nature* 1990; **343**: 651–3

16 Torres M, Hall FL, O'Neill K. Stimulation of human neutrophils with formyl-methionyl-leucyl-phenylalanine induces tyrosine phosphorylation and activation of two distinct mitogen-activated protein-kinases. *J Immunol* 1993; **150**: 1563–77

17 Kuroki M, O'Flaherty JT. Differential effects of a mitogen-activated protein kinase kinase inhibitor on human neutrophil responses to chemotactic factors. *Biochem Biophys Res Commun* 1997; **232**: 474–7

18 Hii CST, Stacey K, Moghaddami N, Murray AW, Ferrante A. Role of the extracellular signal-regulated protein kinase cascade in human neutrophil killing of *Staphylococcus aureus* and *Candida albicans* and in migration. *Infect Immun* 1999; **67**: 1297–302

19 Worthen GS, Avdi N, Buhl AM, Suzuki N, Johnson GL. FMLP activates Ras and Raf in human neutrophils. Potential role in activation of MAP kinase. *J Clin Invest* 1994; **94**: 815–23

20 Boyum A. Isolation of mononuclear cells and gramulocytes from human blood. *Scand J Clin Lab Invest* 1968 (Suppl.); **21**: 77–89

21 Nelson RD, Quie PG, Simmons RL. Chemotaxis under agarose: a new and simple method for measuring chemotaxis and spontaneous migration of human polymorphonuclear leukocytes and monocytes. *J Immunol* 1975; **115**: 1650–6

22 Thompson HL, Shiroo M, Saklatvala J. The chemotactic factor N-formylmethionyl-leucyl-phenylalanine activates microtubule-associated protein 2 (MAP) kinase and a MAP kinase kinase in polymorphonuclear leucocytes. *Biochem J* 1993; **290**: 483–8

23 Heine J, Leuwer M, Scheinichen D, *et al.* Flow cytometry evaluation of the *in vitro* influence of four i.v. anaesthetics on respiratory burst of neutrophils. *Br J Anaesth* 1996; **77**: 387–92

24 Usmani SS, Harper RG, Sia CG, Suntharalingam K, Robeson WR. *In vitro* effect of intralipid on polymorphonuclear leukocyte function in the neonate. *J Pediatr* 1986; **109**: 710–2

25 Zu YL, Qi J, Gilchrist A, *et al.* p38 mitogen-activated protein kinase activation is required for human neutrophil function triggered by TNF-alpha or FMLP stimulation. *J Immunol* 1998; **160**: 1982–9

26 Coffer PJ, Geijsen N, M'Rabet L, *et al.* Comparison of the roles of mitogen-activated protein kinase kinase and phosphatidylinositol 3-kinase signal transduction in neutrophil effector function. *Biochem J* 1998; **329**: 121–30

27 Yasui K, Tsuno T, Miyabayashi M, Yamazaki M, Komiyama A. Effects of high-dose granulocyte colony-stimulating factor on neutrophil functions. *Br J Haematol* 1996; **92**: 571–3

28 Reszka AA, Seger R, Diltz CD, Krebs EG, Fischer EH. Association of mitogen-activated protein kinase with the microtubule cytoskeleton. *Proc Natl Acad Sci USA* 1995; **92**: 8881–5

29 Kuroki M, O'Flaherty JT. Extracellular signal-regulated protein kinase (ERK)-dependent and ERK-independent pathways target STAT3 on serine-727 in human neutrophils stimulated by chemotactic factors and cytokines. *Biochem J* 1999; **341**: 691–6

30 Kahraman S, Kilinc K, Dal D, Erdem K. Propofol attenuates formation of lipid peroxides in tourniquet-induced ischaemia-reperfusion injury. *Br J Anaesth* 1997; **78**: 279–81

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REVIEW ARTICLE

Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex

S. M. Kinsella[1]* and J. P. Tuckey[2]

[1]Sir Humphry Davy Department of Anaesthesia, St Michael's Hospital, Southwell Street, Bristol BS2 8EG, UK. [2]Department of Anaesthesia, Royal United Hospital, Combe Park, Bath BA1 3NG, UK

**Corresponding author*

Reflex cardiovascular depression with vasodilation and bradycardia has been variously termed vasovagal syncope, the Bezold–Jarisch reflex and neurocardiogenic syncope. The circulatory response changes from the normal maintenance of arterial pressure, to parasympathetic activation and sympathetic inhibition, causing hypotension. This change is triggered by reduced cardiac venous return as well as through affective mechanisms such as pain or fear. It is probably mediated in part via afferent nerves from the heart, but also by various non-cardiac baroreceptors which may become paradoxically active. This response may occur during regional anaesthesia, haemorrhage or supine inferior vena cava compression in pregnancy; these factors are additive when combined. In these circumstances hypotension may be more severe than that caused by bradycardia alone, because of unappreciated vasodilation. Treatment includes the restoration of venous return and correction of absolute blood volume deficits. Ephedrine is the most logical choice of single drug to correct the changes because of its combined action on the heart and peripheral blood vessels. Epinephrine must be used early in established cardiac arrest, especially after high regional anaesthesia.

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Vasovagal syncope is loss of consciousness caused by reduced arterial pressure and blood supply to the brain, mediated through neural mechanisms rather than primary cardiac dysfunction. Bradycardia and vasodilation are the characteristic changes that cause systemic hypotension.[48] The trigger may be central, from psychic stress or pain, or may be initiated peripherally by a reduction in venous return to the heart.[94] In daily life this is commonest while the subject is standing. However, the anaesthetist may encounter these reactions during anaesthesia (especially regional), in hypovolaemia and in obstetrics.

The Bezold–Jarisch reflex overlaps with vasovagal syncope. It was initially described as a bradycardic response to injection of various alkaloid compounds, and later found to be mediated by chemoreceptors in the heart.[97] The term has now come to include reactions triggered by cardiac mechanoreceptor activation[58] and it has been used to describe perioperative bradycardia with hypotension.[22 38 51 56 100] A further term in use is neurocardiogenic syncope, which as well as vasovagal syncope includes micturition syncope and carotid sinus syndrome.[9]

Our understanding of these cardiovascular reflexes is fragmentary and complex. Information has been gained from patients and normal volunteers, humans and various other animal species, and using different mechanisms to reduce venous return and activate the reflex.[9 33 58 74 82 86 94 95] This review summarizes present knowledge, emphasizing clinical aspects.

Cause

Haemorrhage

Vasovagal reactions from peripheral stimuli may occur when there is a decrease in venous return, from either hypovolaemia or a redistribution of blood volume. During the Second World War, cardiovascular responses to traumatic and experimental haemorrhage were observed.

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Hypovolaemic hypotensive patients sometimes presented with a slow heart rate.[30] During progressive withdrawal of venous blood, blood pressure was initially maintained by vasoconstriction. With continuing blood loss, there might be a sudden fall in blood pressure, heart rate and peripheral resistance.[62] Barcroft and colleagues found that the incidence of 'fainting' increased as blood loss increased, from 4% after loss of 440 ml to 50% after loss of 1000–1200 ml.[6] An important later clinical finding was that, in cases where haemorrhage presented with relative bradycardia, transfusion alone would reliably increase the heart rate.[47 78]

This pattern of cardiovascular change in response to haemorrhage is unfamiliar, as many textbooks describe a sustained tachycardia mediated via a withdrawal of afferent input from the arterial baroreceptors.[82] This is probably because most hypovolaemic patients respond with a tachycardia, whereas the bradycardic response is noted in a minority only. Textbooks summarize information from a variety of sources, both human non-haemorrhagic models as well as animal experimental data, to produce a coherent picture. However, if the pattern of hypovolaemia presenting with bradycardia were not recognized, some patients may be treated inadequately or inappropriately.[82]

Orthostasis

When a supine individual stands up, 300–800 ml of blood is redistributed from the intrathoracic capacitance vessels to the veins in the lower body. Compensation is needed to maintain venous return to the heart and systemic arterial pressure.[95] Turning a subject into the head-up position on a tilt table induces the change in blood distribution, but without muscle contraction in the legs which assists venous return during standing. Vasovagal syncope is more likely to occur in subjects with a smaller blood volume.[10 25] If a standing subject faints, immediate collapse into the recumbent position will tend to increase venous return towards normal and thus limit the event. However, a severe response can occur if the tilt table is not flattened at the time of a faint.

Compression of inferior vena cava during pregnancy

In late pregnancy some women suffer an acute circulatory collapse, severe enough to mimic haemorrhagic shock, in the supine position.[13 45] Hansen noted that orthostatic hypotension was less common as pregnancy progressed but that 12% of term women had severe hypotension and collapse while supine; this could be reversed by turning to the lateral recumbent position.[37] The cause was identified as compression of the inferior vena cava by the gravid uterus, reducing venous return and right atrial pressure.[47] Further reports of this phenomenon noted that sudden bradycardia occurred in some cases,[45 47] and Lees and co-workers linked this 'supine hypotensive syndrome of pregnancy' with vasovagal fainting.[47]

Regional anaesthesia

Spinal and epidural anaesthesia can prevent reflex vasoconstriction in the blocked segments. Although some hypotension is normal after high regional anaesthesia, if venous return is inadequate because of reduced blood volume or head-up tilting (reverse Trendelenberg), syncope and abrupt bradycardia or sinus arrest can occur.[12 42 79]

Afferent pathways

Cardiac

Some chemical stimuli within the heart activate unmyelinated sensory nerve fibres that pass via the vagus nerve to the brainstem. This causes a vasodepressor response, the classical Bezold–Jarisch reflex.[33] The cardiac site of origin in humans was demonstrated in heart-transplant patients. Coronary artery angiography caused bradycardia in control subjects. On the other hand, the same stimulus resulted in a tachycardia in the residual sinus node tissue of subjects who had the afferent nerves from the heart interrupted by transplantation.[4]

Other unmyelinated afferents are activated via mechanoreceptors which are usually sensitive to left ventricular distension, but may also respond to hypovolaemia.[58] A response to hypovolaemia can occur because, if there is myocardial stimulation combined with underfilling, deformation of the cardiac wall triggers mechanically sensitive nerves in the same way as stretching. The origin of vasovagal responses from cardiac afferents was proposed by Oberg and Thoren.[69] They found that both cardiac afferents and arterial baroreceptors cause circulatory compensation during haemorrhage in cats, but only the cardiac afferents caused bradycardia during rapid haemorrhage, a 'vago-vagal reflex'.[70] Ludbrook and Ventura showed that when venous return was progressively reduced in rabbits by inflation of a cuff round the vena cava, arterial baroreceptors mediated the compensatory phase and cardiac afferents were usually involved in the depressor phase.[55]

Non-cardiac

Other evidence, also from patients who have had heart transplants, seems to contradict this 'cardiac' theory of the vasodepressor response in humans. In a number of cases, syncopal reactions have been noted in spite of evidence that reinnervation had not occurred.[27 49 80] Evidence for differences between species comes from experiments in dogs, where sympathetic withdrawal occurring during haemorrhagic hypotension was mediated neither by aortic baroreceptors nor by cardiac nerves.[65] Even in species with good evidence of a cardiac origin for the inhibitory response, the heart may not be the only source. Cardiac afferent nerve block in rabbits did not reliably inhibit the sympathoinhibitory phase during constriction of the inferior vena

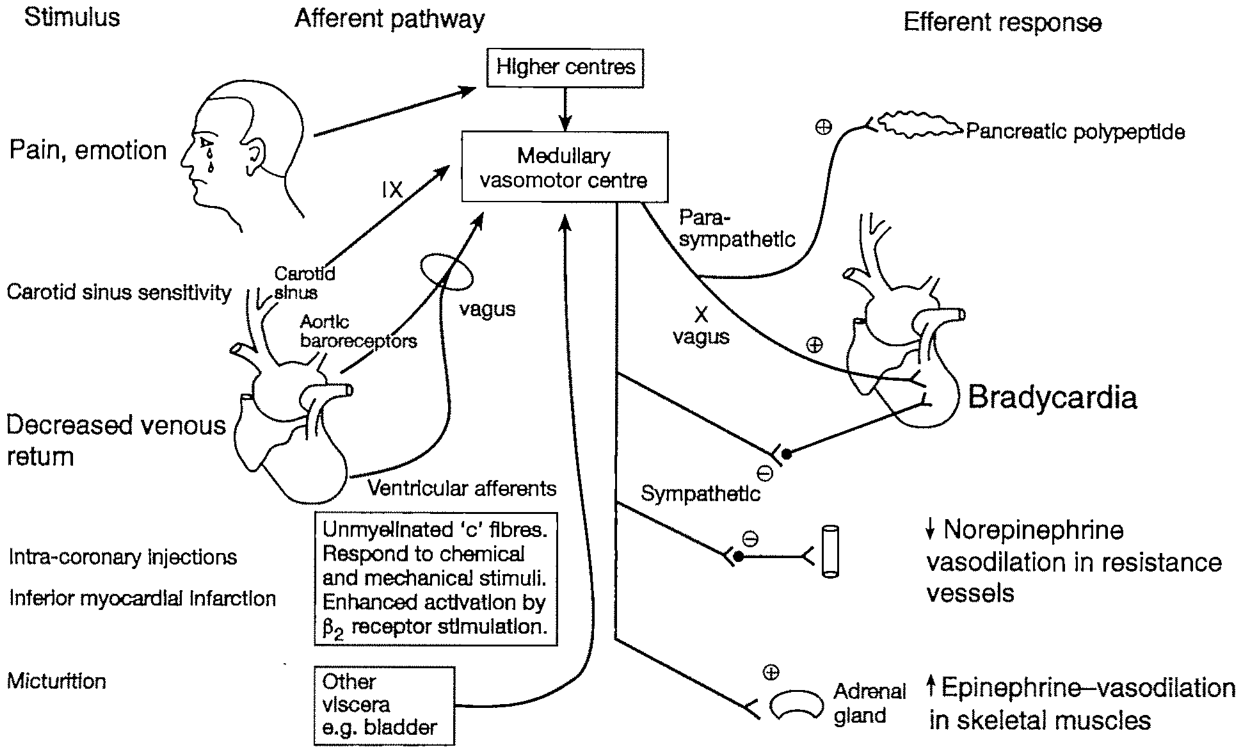
Stimulus
Afferent pathway
Efferent response
Higher centres
Pain, emotion
Medullary vasomotor centre
IX
Pancreatic polypeptide
Para-sympathetic
Carotid sinus sensitivity
Carotid sinus
Aortic baroreceptors
vagus
X vagus
Bradycardia
Decreased venous return
Ventricular afferents
Sympathetic
Intra-coronary injections
Inferior myocardial infarction
Unmyelinated 'c' fibres. Respond to chemical and mechanical stimuli. Enhanced activation by β2 receptor stimulation.
↓ Norepinephrine vasodilation in resistance vessels
Micturition
Other viscera e.g. bladder
Adrenal gland
↑ Epinephrine–vasodilation in skeletal muscles

Fig 1 Neurally mediated syncope. IX, glossopharyngeal nerve; X, vagus nerve; ⊕, stimulates; ⊖, inhibits.

cava, indicating that there are sites of origin for this reflex other than the heart.[55]

An alternative mechanism of triggering vasodepressor reflexes could be via arterial baroreceptors. Baroreceptor activation, secondary to increases in blood pressure, decreases sympathetic outflow and increases parasympathetic activity, leading to vasodilation and bradycardia. With a decrease in blood pressure, baroreceptor activity ceases, but with progressive hypovolaemia there may be paradoxical recurrence of baroreceptor discharge, so-called 'collapse firing' (Fig. 1).[95]

Central transmission

Arterial baroreceptor and cardiac afferents enter the brain via the glossopharyngeal and vagus nerves, and synapse in the nucleus tractus solitarius and the ventrolateral medulla.[64] Arterial baroreceptor afferents may have a closer integration with mechanically sensitive than with chemosensitive cardiac afferents.[72 96] Although there is some overlap, cardiac afferents that are mechanically sensitive may tend to be more concerned with circulatory homeostasis whereas chemosensitive afferents are activated by cardiac pathology.[72]

Some syncopal reactions are initiated by emotional factors. It is known that the limbic system is concerned with emotions, and in some animal species stimulation of the limbic sympatho-inhibitory centre causes hypotension and bradycardia.[94] Once a reaction has started, orthostatic stress in the erect position will augment any central effects. Strong emotions also cause sympathetic nervous system activation. The role of sympathetic stimulation in syncope, especially with regard to concentrations of circulating epinephrine, is noted in the next section.

There is evidence that endogenous opioids are important neurotransmitters in the nucleus tractus solitarius[46] and are involved in the syncopal response in animals.[93] This has generated particular interest because of the frequent clinical use of opioids and opioid antagonists and the hope that prevention or treatment strategies might be directed here.[54 93] Blockade of cardiac afferent nerves prevented decompensation during simulated haemorrhage in rabbits; the same effect was also achieved by injecting extremely low doses of naloxone into the fourth ventricle.[26] However, in humans, intravenous naloxone pre-treatment did not alter vasovagal responses to lower-body negative pressure.[28 85] The δ receptor subtype may be more important than the μ receptor, and therefore δ-specific antagonists may show more benefit.[93]

Efferent responses

During vasovagal syncope, the efferent responses are increased vagal activity, especially to the heart, and decreased sympathetic activity. The resulting combination of bradycardia and vasodilation causes significant hypotension. Stroke volume and cardiac output generally decline further.[95] The vasovagal response with bradycardia and afterload reduction may protect the heart when the myocardial oxygen supply is compromised,[94] at the expense of the overall need to maintain systemic arterial pressure and cardiac output. With tilt-induced vasovagal syncope, most cases show both cardiac and vascular components but a few may show either a predominantly bradycardic or vasodepressor response.[89]

Increased parasympathetic activity is not selective for the heart, as pancreatic polypeptide titres increase during haemorrhage[78] and presyncope[42 79] indicating a more general parasympathetic activation. The gastrointestinal effects probably account for the nausea accompanying vasovagal syncope and possibly an increase in splanchnic blood flow.[3]

Lewis postulated that there was a vascular component to fainting reactions, as the associated hypotension was not reversed when atropine was administered to correct the bradycardia.[48] Studies of forearm blood flow using venous occlusion plethysmography and cardiac output[6 13] confirmed this. An increase in forearm blood flow was found at the time of fainting induced by table tilting, the exaggerated lordotic posture and spinal anaesthesia.[13]

The vasodilation is caused by sympathetic inhibition. During haemodialysis, presyncope was associated with increased sympathetic nerve activity and calf vascular resistance and decreased calf blood flow. Syncope with hypotension and bradycardia came with decreased sympathetic nerve activity and vascular resistance. Calf blood flow did not change because of the simultaneous reduction in blood pressure and resistance.[19]

The importance of the vascular component was shown during near-syncope in a heart-transplanted patient. Although the contraction frequency of the transplanted ventricle increased, hypotension occurred associated with decreased sympathetic nerve activity.[80] It has been suggested that sympathetic 'switch-off' with reduced systemic vascular resistance and hypotension may normally precede the change in heart rate at syncope.[74]

The decrease in sympathetic nerve activity before or during syncope is followed by decreased concentrations of norepinephrine.[94 101] However epinephrine concentrations increase, causing muscle vasodilation and tending to reduce systemic vascular resistance further.[94 101] Exogenous β-agonists may also increase the tendency to vasovagal reactions.[1] At the same time as most tissues show a decrease in vascular resistance, there is evidence of cerebral vasoconstriction in presyncope and syncope.[9 34 41] The significance of this is unclear.[9]

Anaesthesia

General anaesthesia

Modern anaesthetic agents do not have anticholinergic or sympathomimetic side effects. Simple 'vagal' (as opposed to vasovagal) reflexes with bradycardia and transient asystole are more common, especially during ophthalmic or pelvic surgery. Bradycardia characteristically resolves quickly when the stimulus ceases. Generally, hypotension will only occur if bradycardia is extreme. It is presumed that there is no component of vascular dilation.[84]

True vasovagal reactions have been described around the time of induction of general anaesthesia,[24 35 36 38 44] associated with anxiety and pain of venepuncture. When full cardiovascular monitoring has preceded venous cannulation, asystole has been noted of several minutes' duration, requiring cardiopulmonary resuscitation.[36 38 44] The patient may give a history of syncopal attacks during venepuncture or minor surgery.[36 38] If the syncopal reaction is delayed for a short time, then anaesthetic drugs may also be given, which will complicate the diagnosis considerably.[24 35] Compensated hypovolaemia may become evident after induction of anaesthesia.[77]

Spinal and epidural anaesthesia

Pain and anxiety may cause fainting during induction of regional anaesthesia as with general anaesthesia.[61 87] Case reports note a history of fainting, as well as the added influence of orthostatic stress from the sitting position used for needle insertion.[61 87]

Haemodynamic instability is expected with the onset of the block, but delayed bradycardia or asystole may be more sinister. Although fatalities associated with regional anaesthesia are usually found in the elderly and those with co-morbidity,[5 71] the landmark report by Caplan and colleagues[16] indicated a risk even in healthy patients. These authors reviewed 14 cases of cardiac arrest leading to death or severe brain damage in patients having spinal anaesthesia. Cases were identified from a database of over 900 closed insurance claims during 1978–1986. All but one case occurred during surgery after the block had been established for some time. The average upper limit of sensory block was T4.

In the time leading up to the arrest, heart rate and blood pressure showed a gradual decline. The last assessment of apparently adequate ventilation and circulation was followed, on average in <2 min, by the first clue of problems. This 'first clue' was bradycardia, hypotension, cyanosis or loss of consciousness, in descending order of frequency. Cardiac arrest comprised either asystole or severe bradycardia with loss of output.

Caplan and colleagues[16] suspected two aspects of management which might have been responsible for these devastating outcomes. The first was the use of central depressant drugs in addition to the regional anaesthesia. Twelve patients had had at least one but usually more than one intravenous opioid or sedative, including fentanyl, diazepam, droperidol and thiopentone. Half the patients were in a sleep-like state. Besides a contribution from unappreciated respiratory depression, the authors 'speculated that circulatory changes related to high sympathetic block' were an important factor. The authors also highlighted possible deficiencies in the treatment of the cardiac arrest. On average, epinephrine was not given until 6 min after the start of cardiopulmonary resuscitation and 8 min after the first clue of impending arrest.

These descriptions suggest vasovagal reactions after a critical reduction in venous return. Regional anaesthesia may have affected the physiological responses so that cardiac arrest was sustained. Hypertension and tachycardia in response to hypoxia do not occur during epidural anaesthesia in dogs, probably because of sympathetic block.[73] Furthermore, coronary perfusion pressure gradient (which indicates the likelihood of successful resuscitation attempts) during ventricular fibrillation in dogs was significantly reduced after high spinal anaesthesia.[76]

Caplan and colleagues[16] acknowledged that these cases were likely to be a biased sample of all those patients who develop cardiac arrest during spinal anaesthesia, as they came from medicolegal sources. This is borne out by the subsequent publication of cases of bradycardia or brief asystole in association with epidural or spinal anaesthesia, which seemed to start in the same way but have successful outcomes.[14 29 50 56] Spinal block height was often at the upper thoracic level,[14 29] whereas epidural analgesia was induced with large doses of local anaesthetic.[29 50] Deep sedation was not used.[29 50] Although some episodes occurred soon after induction of anaesthesia, most started during the operation and two developed only in the post-operative recovery ward.[29 50]

The 'event' that was noted was a sudden decrease in heart rate, although often a gradual decline in heart rate during stable anaesthesia had preceded this.[56] Bradycardia was reversed with atropine initially in all subjects, but ephedrine, epinephrine and external cardiac massage were also needed in some cases. None of these patients suffered morbidity after the event, reinforcing Caplan and colleagues' suggestion[16] that immediate treatment of bradycardia or asystole under these circumstances is crucial.

An aspect of management that may have contributed to the event in some cases was the use of infusions of epinephrine to maintain cardiac output and sodium nitroprusside to induce hypotension.[50] Decreases in cardiac filling pressure were recorded or surmised in several cases. Both β-stimulants[1] and nitroprusside[99] have been implicated in inducing vasovagal reactions.

Two prospective studies examined the prevalence and risk factors for bradycardia and other intraoperative complications during spinal anaesthesia, in a total of 2700 patients.[17 90] Bradycardia occurred in 10%, hypotension in 22% and nausea in 10%. No patients developed asystole. The most important factor implicated in all of these complications was dermatomal block to T5/6 or higher. Bradycardia was more likely with young age or ASA 1 physical status, in contrast to hypotension found more frequently in the elderly. Bradycardia defined as a decrease below a threshold (heart rate <50 beats min^{-1}) is consistent with cardiac sympathetic nerve inhibition associated with mid-thoracic block level.[32] However, the development of sudden bradycardia over a few heartbeats, and the potential for the reversal of bradycardia by postural changes that increase venous return, can only be explained by a vasovagal reaction.[32]

In summary, spinal and epidural anaesthesia are not infrequently associated with bradycardia or hypotension defined by crossing a particular threshold level for rate or arterial pressure.[17 90] Less frequently, vasovagal reactions with sudden bradycardia or asystole occur, initiated by reduced venous return and therefore more likely with high block level and hypovolaemia. Outcomes are usually good, but delays in instituting corrective treatment and resuscitation may cause permanent cerebral damage or death.[16] The risk of asystole extends into the post-operative phase.[50] The risk of life-threatening vasovagal reactions during regional anaesthesia may be in the order of three per 1000,[29] compared with 5% of patients who have both bradycardia and hypotension during spinal anaesthesia.[17]

Obstetric anaesthesia

An early report of supine hypotensive syndrome in pregnancy describes a woman who had a Caesarean section because it was thought that she was hypovolaemic secondary to a ruptured uterus.[63] The syndrome is not usually of serious consequence in isolation, because once recognized it is rapidly relieved by a change in position. However, regional anaesthesia combined with inferior vena cava compression introduces significant risk because of interference with cardiovascular control, and the inability of the patient to move herself. Holmes reviewed the literature from the 1930s to the 1950s on maternal mortality during Caesarean section with spinal anaesthesia. Problems occurred soon after the patient was moved into the supine position, as the sympathetic block developed. Sudden bradycardia was found in cases when heart rate was recorded.[39 40] Holmes suggested that unappreciated compression of the vena cava was the likely cause, rather than other possibilities such as respiratory insufficiency.[39] The risk is present even without the sympathetic block induced by regional anaesthesia: a patient with severe pre-operative supine hypotension died after induction of general anaesthesia.[20] These life-threatening reactions are now rare since the introduction of lateral tilt during Caesarean section, but cases still occur despite these precautions.[2 60 81 100]

Interscalene block for shoulder surgery

New surgical techniques present new anaesthetic problems and challenges. A recent development is the practice of shoulder arthroscopy in the sitting position, using interscalene block for anaesthesia.[22 43 51] D'Alessio and colleagues[22] reported vasovagal events, defined as hypotension or bradycardia requiring treatment, in 20 of 116 patients who had surgery in this way. Epinephrine was used for the interscalene block as well as for injection into the surgical incision sites and joint irrigation. Patients who received higher doses of epinephrine were more likely to belong either to the vasovagal group or to a subset of the non-vasovagal group who were given β-adrenergic blockers for treatment of tachycardia or hypertension (n=18). Intraoperative peak heart rate was higher in these two groups than in those without problems. The authors suggested that the Bezold–Jarisch reflex resulted from a combination of awake surgery in the sitting position with augmentation of the cardiovascular stress as a result of the β-agonist effects of epinephrine reducing systemic vascular resistance and stimulating the myocardium. The patients who received β-antagonist treatment for tachycardia or hypertension were protected from this. This finding was supported by a randomized study comparing treatment with metoprolol, glycopyrrolate or placebo after surgical positioning.[51] Hypotensive or bradycardic events, or both, were found in only 5% of the group treated with metoprolol; this was significantly lower than the incidences in the placebo and glycopyrrolate groups (28% and 22%, respectively).

Expression of syncopal reactions

The identification of a minority of patients who demonstrate vasovagal responses during haemorrhage or regional anaesthesia might suggest that these individuals are qualitatively different. Development of the tilt table and lower-body negative pressure devices allowed standardized and repeatable testing, with the hope of distinguishing 'normal' and 'abnormal' individuals. Although syncope thresholds vary among individuals,[10 66] a number of factors prevent a simple division of the population into two groups. Tilt-table testing may provoke syncope in otherwise asymptomatic subjects. On the other hand, patients with a clinical history may not demonstrate problems even with provocative testing such as isoprenaline infusions in addition to head-up tilt. Besides this, syncope in a given subject may be expressed to a different degree when tested using the same method on different occasions,[9] and may be provoked by one stressor but not another.[19]

The amount by which cardiac output is reduced at the time of vasovagal syncope depends on experimental design and the method by which it is induced.[95] At one time the trigger for syncope was believed to be 'contractions of an almost empty ventricle' causing stimulation of left ventricular mechanoreceptors.[69] This has not been studied during clinical blood loss, but the bulk of evidence from experimental syncope does not support this suggestion. Although one study found that baseline left ventricular fractional shortening during systole increased from 23% in the supine position to 51% at the onset of syncope during head-up tilt,[83] another found no difference in cardiac volume preceding tilt-induced syncope.[68] Two studies of the effects of epidural anaesthesia also did not demonstrate significant cardiac underfilling: Sander-Jensen and colleagues found a 25% reduction in end-systolic volume at bradycardia,[79] while Jacobsen and co-workers found only a 13% reduction in left ventricular diameters at the onset of presyncopal symptoms.[42]

Does an explanation lie in the experimental design? Hypovolaemia and the standing position may be counted as 'natural' stresses which the circulatory reflexes are designed to counteract, but head-up tilt and epidurals affect the integrated cardiovascular response to reduced venous return. During head-up tilt the leg muscles do not contract and therefore the 'muscle pump' that augments venous return is inactive, so that vasovagal reactions can occur in subjects who do not give a clinical history.[94] Epidural anaesthesia inhibits not only the muscle pump but also compensatory veno- and arterioconstriction.

We conclude that there is no true separation between normal and abnormal, but a range of individual susceptibility to vasovagal reactions from those who may have life-threatening problems during their daily life[57] to those who do not respond to provocative testing. A patient may show syncope in some circumstances but not in others.

Implications for anaesthetic management

We consider that a pragmatic approach in clinical practice is to separate patients on the basis of whether or not they have a history of syncopal episodes.

Anaesthetic management of the patient with known syncope

A detailed history may provide a pattern to the attacks, precipitating factors, the severity and any previous medical investigations. Sometimes syncopal episodes are specifically related to venepuncture and general anaesthetic induction.[36 38] Cardiological investigation may be appropriate, although prophylactic treatment in general is not very effective.

In mild cases it is probably appropriate merely to apply full non-invasive cardiovascular monitoring before doing anything painful. However, management of severe cases must be planned carefully. We would consider oral premedication with a sedative and an anticholinergic.[44] Topical local anaesthetic cream for the venepuncture site[44] may be used before intravenous induction, or an inhalational induction of anaesthesia.[38] Drugs implicated in the genesis of asystole include propofol, fentanyl, suxamethonium and vecuronium.

During the maintenance of general anaesthesia, vasovagal syncope does not occur.[84] However bradycardia in response to perioperative bleeding has been noted during neurolept anaesthesia.[75]

If regional anaesthesia is being performed, similar considerations apply as for induction of general anaesthesia. The lateral position for insertion of a spinal or epidural is preferable to the sitting position.[61 87]

Management of spinal and epidural anaesthesia in patients with no history of syncope

Block height

The incidence of baseline bradycardia is greater if the block extends above the mid-thoracic region.[17 90] A high block may increase the risk of a vasovagal reaction in several ways. There may be direct cardiac sympathetic inhibition and decreased territory for compensatory vasoconstriction.[11] Indirect effects include deafferentation (see below) and ventilatory impairment. Although block height cannot be precisely controlled, especially with a single-shot technique, important factors during spinal administration that are within the control of the anaesthetist include drug dose, baricity and patient positioning.[31 88]

Sedation and breathing

Although episodes of bradycardia may occur during regional anaesthesia in the absence of sedation,[16 50] oversedation may increase the risk.[16 73] Hypnotic drugs should be given to obtain anxiolysis rather than deep sedation. The patient who is able to communicate symptoms may give an early warning of the development of a vasovagal reaction. The effective dose of midazolam, propofol and thiopentone is reduced by 40–75% during spinal anaesthesia, possibly as a result of deafferentation caused by the regional block.[8 91 92] Opioids should be reserved for intraoperative discomfort or pain.

Hypoxaemia may occur during high regional anaesthesia because of hypoventilation, or a reduction in cardiac output causing 'shunt effect'. Prophylactic oxygen administration should be considered. Pulse oximetry is helpful, and end-tidal carbon dioxide can be monitored even in unintubated patients using a sidestream capnograph.

Circulating volume status and body position

Pre-existing hypovolaemia before induction of regional anaesthesia may lead to cardiovascular collapse.[12] Compensatory vasoconstriction in unblocked regions of the body maintains peripheral resistance with epidural blocks up to the T5 level,[11] but passive venous return is crucial in this situation. Intraoperative blood loss must be meticulously replaced.

Changing from a head-down position to horizontal can precipitate cardiac arrest,[67] whereas asystole[61] may be reversed by lowering the heart relative to the lower body. Greene and Brull[32] emphasize the necessity of using a slight head-down position during spinal-induced hypotension.

Pharmacological prophylaxis

The treatment of bradycardia of gradual onset during regional anaesthesia will depend on the associated blood pressure as well as the clinical and surgical situation. However, it is not possible reliably to prevent a vasovagal reaction by keeping above a particular heart-rate threshold, as such a reaction may occur after a period of normal heart rate or tachycardia.[50]

Treatment

During general anaesthesia, simple vagal reactions will usually respond to stopping the stimulus. However, when a vasovagal reaction is suspected during regional anaesthesia, then the cardiovascular change is augmented by vasodilation and is likely to lead to significant hypotension. Restoration of venous return is urgent as spontaneous recovery from asystole may occur if this is achieved,[61] although drug treatment must not be delayed. Head-down tilt or leg elevation should be used,[16] and compression of the vena cava should be relieved in obstetric cases.[39 40] Intravenous fluids must be considered if there is any suspicion of hypovolaemia; a rapidly running infusion will hasten the transit of drugs into the central circulation. However, it is essential to distinguish between true hypovolaemia resulting from blood or fluid loss and a shift of blood from central to peripheral compartments. Vasovagal syncope may occur after a relatively small reduction in cardiac volume during epidural anaesthesia.[42 79]

Anticholinergic drugs are often the first treatment for slow heart rate during anaesthesia, especially general anaesthesia. Although atropine has been used as the only agent to treat asystole during regional anaesthesia,[56] it may not be the best single agent if bradycardia is suspected to be accompanied by vasodilation. Hypotension during vasovagal syncope may persist after the relief of bradycardia by atropine.[48]

Sympathomimetic drugs, by contrast, will counteract the vasodilation in both the arterial and venous circulations. Commonly used agents are either ephedrine or various selective α-agonists. Most assessments have been in the context of prophylaxis and treatment of hypotension during regional anaesthesia, with the authors drawing different conclusions. One study found that ephedrine was less effective than metaraminol at reversing hypotension and decreases in central venous pressure and systemic vascular resistance index. Metaraminol, on the other hand, decreased the heart rate.[21] However, Butterworth and colleagues showed that both ephedrine and phenylephrine increased blood pressure effectively, but only ephedrine decreased venous capacitance.[15] Starting with a low heart rate, the direct sympathetic effects on the heart rate of ephedrine are advantageous, whereas, if baroreceptor function remains active,[59] an α-agonist might reduce it further. However if hypotension persists after adequate doses of ephedrine, or epinephrine-containing epidural solutions, an α-agonist might be considered.

Successful use of thump pacing for asystole during regional anaesthesia has been described.[50] However, once persisting cardiac arrest occurs, external cardiac massage must be started to ensure circulation of resuscitation drugs and perfusion of vital organs. Prompt treatment with epinephrine has been emphasized as crucial for successful recovery.[14 16 50] A study in dogs has suggested that above-normal doses of epinephrine may be necessary during cardiac arrest in association with high spinal anaesthesia.[76]

A standard sequence using atropine, ephedrine and then epinephrine to treat bradycardia during spinal anaesthesia has been advocated.[14] Although flexibility is necessary, we suggest that ephedrine is the most logical choice for a single agent to treat profound bradycardia or asystole during regional anaesthesia, given the lack of vasoconstrictor effect of atropine and the potential for heart rate reduction with α-agonists. For asystole or persistent severe bradycardia, epinephrine should be used early.

Future research

Ideally patients who are likely to have vasovagal reactions during anaesthesia could be identified before surgery, but this is unlikely for several reasons. It has been noted that many subjects who develop vasovagal reactions in daily life are at merely one end of a spectrum of cardiovascular control,[9] with a minority suffering life-threatening events.[57] Provocation tests such as the tilt table give variable results on repeated testing.[9] Prophylactic treatment is unreliable, although recent advances in pacemaker technology are promising.[18]

The extent of the problem needs clearer definition.[29] General risk factors for bradycardia during spinal anaesthesia, such as block height and young age, have been elucidated,[17 90] but the identification of severe bradycardic-hypotensive events may need a different approach, such as critical incident reporting.[60]

Analysis of heart-rate variability, which gives a measure of the absolute and relative activity of the sympathetic and parasympathetic systems, has shown differences in syncopal and non-syncopal subjects.[52] The drawback is that several minutes of recording are needed for analysis. However, recent approaches such as complex demodulation, which allow pattern recognition over a much shorter time-scale, might be more applicable to clinical practice.[53] If a presyncopal state could be reliably identified, this might allow monitoring not only perioperatively but also into the recovery period.[50]

The assumption that there is a vascular component to sudden hypotension and bradycardia during anaesthesia and with tilt-table testing has often been made, whereas the use of direct measurements has been limited to experimental situations.[6 13 19] It has been noted that the efferent expression of vasovagal reactions may include primarily cardiac slowing, vasodilation or a mixed pattern. To identify the haemodynamic changes occurring during bradycardic episodes, it is essential to monitor whether there is accompanying vasodilation. This is only likely to be feasible during clinical practice if non-invasive methods are used. In the past, monitoring of vasoconstrictor tone has been performed, albeit crudely, with photoelectric plethysmography.[23] Experimentally, plethysmographic amplitude increases markedly at the time that sympathetic nerve activity decreases during syncope.[98] The principle of photoelectric plethysmography is used as the basis of pulse oximetry.

References

1 Almquist A, Goldenberg IF, Milstein S. *et al.* Provocation of bradycardia and hypotension by isoprotenerol and upright posture in patients with unexplained syncope. *New Engl J Med* 1989; **320**: 346–51

2 Anon. *Why Mothers Die: Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996.* Norwich: HMSO, 1998

3 Arndt JO, Hock A, Stanton-Hicks M, Stuhmeier K-D. Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–23

4 Arrowood JA, Mohanty PK, Hodgson JM, Dibner-Dunlap ME, Thames MD. Ventricular sensory endings mediate reflex bradycardia during coronary arteriography in humans. *Circulation* 1989; **80**: 1293–300

5 Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia. Results of a prospective survey in France. *Anesthesiology* 1997; **87**: 479–86

6 Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer EP. Post haemorrhagic fainting. Study by cardiac output and forearm flow. *Lancet* 1944; **i**: 489–91

7 Barriot P, Riou B. Hemorrhagic shock with paradoxical bradycardia. *Intensive Care Med* 1987; **13**: 203–7

8 Ben-David B, Vaida S, Gaitini L. The influence of high spinal anesthesia on sensitivity to midazolam sedation. *Anesth Analg* 1995; **81**: 525–8

9 Benditt DG, Erickson M, Gammage MD, Markowitz T, Sutton R. A synopsis: neurocardiogenic syncope, an international symposium, 1996. *Pacing Clin Electrophysiol* 1997; **20**: 851–60

10 Bergenwald L, Freyschuss U, Sjostrand T. The mechanism of orthostatic and haemorrhage fainting. *Scand J Clin Lab Invest* 1977; **37**: 209–16

11 Bonica JJ, Berges PU, Morikawa K. Circulatory effects of peridural block: I. Effects of level of analgesia and dose of lidocaine. *Anesthesiology* 1970; **33**: 619–26

12 Bonica JJ, Kennedy WF, Akamatsu TJ, Gerbershagen HU. Circulatory effects of peridural block: III. Effects of acute blood loss. *Anesthesiology* 1972; **36**: 219–27

13 Brigden W, Howarth S, Sharpey-Schafer EP. Postural changes in the peripheral blood-flow of normal subjects with observations on vasovagal fainting reactions as a result of tilting, the lordotic posture, pregancy and spinal anaesthesia. *Clin Sci* 1950; **9**: 79–91

14 Brown DL, Carpenter RL, Moore DC *et al.* Cardiac arrest during spinal anesthesia. *Anesthesiology* 1988; **68**: 971–2

15 Butterworth JF, Piccione W, Berrizbeitia LD, Dance G, Shemin RJ, Cohn LH. Augmentation of venous return by adrenergic agonists during spinal anesthesia. *Anesth Analg* 1986; **65**: 612–6

16 Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology* 1988; **68**: 5–11

17 Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. *Anesthesiology* 1992; **76**: 906–16

18 Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999; **33**: 16–20

19 Converse RL, Jacobsen TN, Jost CMT *et al.* Paradoxical

withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest* 1992; **90**: 1657–65

20 Courtney L. Supine hypotensive syndrome during Caesarean section. *Br Med J* 1970; i: 797–8

21 Critchley LAH, Short TG, Gin T. Hypotension during subarachnoid anaesthesia: haemodynamic analysis of three treatments. *Br J Anaesth* 1994; **72**: 151–5

22 D'Alessio JG, Weller RS, Rosenblum M. Activation of the Bezold–Jarisch reflex in the sitting position for shoulder arthroscopy using interscalene block. *Anesth Analg* 1995; **80**: 1158–62

23 Dorlas JC, Nijboer JA. Photo-electric plethysmography as a monitoring device in anaesthesia. Application and interpretation. *Br J Anaesth* 1985; **57**: 524–30

24 Dorrington KL. Asystole with convulsion following a subanaesthetic dose of propofol plus fentanyl. *Anaesthesia* 1989; **44**: 658–9

25 El-Sayed H, Hainsworth R. Relationship between plasma volume, carotid baroreceptor sensitivity and orthostatic tolerance. *Clin Sci* 1995; **88**: 463–70

26 Evans RG, Ludbrook J, Potocnik SJ. Intracisternal naloxone and cardiac nerve blockade prevent vasodilatation during simulated haemorrhage in awake rabbits. *J Physiol* 1989; **409**: 1–14

27 Fitzpatrick AP, Banner N, Cheng A, Yacoub M, Sutton R. Vasovagal reactions may occur after orthotopic heart transplantation. *J Am Coll Cardiol* 1993; **21**: 1132–7

28 Foldager N, Bonde-Petersen F. Human cardiovascular reactions to simulated hypovolaemia, modified by the opiate antagonist naloxone. *Eur J Appl Physiol* 1988; **57**: 507–13

29 Geffin B, Shapiro L. Sinus bradycardia and asystole during spinal and epidural anesthesia: a report of 13 cases. *J Clin Anesth* 1998; **10**: 278–85

30 Grant RT, Reeve EB. Clinical observations on air-raid casualties. *Br Med J* 1941; ii: 293–7

31 Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; **64**: 715–30

32 Greene NM, Brull SJ. *Physiology of Spinal Anesthesia*, 4th edn. Baltimore, MD: Williams and Wilkins, 1994

33 Grimm DR. Neurally mediated syncope: a review of cardiac and arterial receptors. *J Clin Neurophysiol* 1997; **14**: 170–82

34 Grubb BP, Gerard G, Roush K *et al.* Cerebral vasoconstriction during head-upright tilt-induced vasovagal syncope. A paradoxic and unexpected response. *Circulation* 1991; **84**: 1157–64

35 Guise PA. Asystole following propofol and fentanyl in an anxious patient. *Anaesth Intensive Care* 1991; **19**: 116–18

36 Hampl KF, Schneider MC. Vasovagal asystole before induction of general anaesthesia. *Eur J Anaesth* 1994; **11**: 131–3

37 Hansen R. Ohnmacht und Schwangerschaft. *Klin Wochenschr* 1942; **21**: 241–5

38 Hart PS, Yanny W. Needle phobia and malignant vasovagal syndrome. *Anaesthesia* 1998; **53**: 1002–4.

39 Holmes F. Spinal analgesia and Caesarean section. Maternal mortality. *J Obstet Gynaecol Br Emp* 1957; **64**: 229–32

40 Holmes F. The supine hypotensive syndrome. Its importance to the anaesthetist. *Anaesthesia* 1960; **15**: 298–306

41 Ikeda T, Ohbuchi H, Ikenoue T, Mori N. Maternal cerebral hemodynamics in the supine hypotensive syndrome. *Obstet Gynecol* 1992; **79**: 27–31

42 Jacobsen J, Sofelt S, Brocks V, Fernandes A, Warberg J, Secher NH. Reduced left ventricular diameters at onset of bradycardia during epidural anaesthesia. *Acta Anaesthesiol Scand* 1992; **36**: 831–6

43 Kahn RL, Hargett MJ. β-Adrenergic blockers and vasovagal episodes during shoulder surgery in the sitting position under interscalene block. *Anesth Analg* 1999; **88**: 378–81

44 Keane TK, Hennis PJ, Bink-Boelkens MTE. Non-drug related asystole associated with anaesthetic induction. *Anaesthesia* 1991; **46**: 38–9

45 Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstet Gynecol* 1994; **83**: 774–88

46 Lawrence AJ, Jarrott B. Neurochemical modulation of cardiovascular control in the nucleus tractus solitarius. *Prog Neurobiol* 1996; **48**: 21–53

47 Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. *Clin Sci* 1967; **32**: 453–65

48 Lewis T. Vasovagal syncope and the carotid sinus mechanism with comments on Gowers's and Nothnagel's syndrome. *Br Med J* 1932; i: 873–6

49 Lightfoot JT, Rowe SA, Fortney SM. Occurrence of presyncope in subjects without ventricular innervation. *Clin Sci* 1993; **85**: 695–700

50 Liguori GA, Sharrock NE. Asystole and severe bradycardia during epidural anesthesia in orthopedic patients. *Anaesthesiology* 1997; **86**: 250–7

51 Liguori GA, Kahn RL, Gordon J, Gordon MA, Urban MK. The use of metoprolol and glycopyrrolate to prevent hypotensive/bradycardic events during shoulder arthroscopy in the sitting position under interscalene block. *Anesth Analg* 1998; **87**: 1320–5

52 Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. *Circulation* 1990; **81**: 1803–10

53 Lipsitz LA, Hayano J, Sakata S, Okada A, Morin RJ. Complex demodulation of cardiorespiratory dynamics preceding vasovagal syncope. *Circulation* 1998; **98**: 977–83

54 Ludbrook J. Faint heart. *Br Med J* 1989; **298**: 1054–5

55 Ludbrook J, Ventura S. Roles of carotid baroreceptor and cardiac afferents in hemodynamic responses to acute central hypovolaemia. *Am J Physiol* 1996; **270**: H1538–48

56 Mackey DC, Carpenter RL, Thompson GE, Brown DL, Bodily MN. Bradycardia and asystole during spinal anesthesia: a report of three cases without morbidity. *Anesthesiology* 1989; **70**: 866–8

57 Maloney JD, Jaeger FJ, Fouad-Tarazi FM, Morris HH. Malignant vasovagal syncope: prolonged asystole provoked by head-up tilt. *Cleveland Clin J Med* 1988; **55**: 542–8

58 Mark AL. The Bezold Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983; **1**: 90–102

59 Mark AL. Cardiopulmonary baroreflexes in humans. In: Shepherd JT, Abboud FM, eds. *Handbook of Physiology*, Section 2: *The Cardiovascular System*, Vol. III. Bethesda, MD: American Physiological Society, 1983: 795–813

60 McBrien ME, Bali IM. Untoward incident reporting in obstetric anaesthesia: a 6-month prospective study in Northern Ireland. *Int J Obstet Anesth* 1996; **5**: 225–8

61 McConachie I. Vasovagal asystole during spinal anaesthesia. *Anaesthesia* 1991; **46**: 281–2

62 McMichael J. Clinical aspects of shock. *J Am Med Assoc* 1944; **124**: 275–81

63 McRoberts WA. Postural shock in pregnancy. *Am J Obstet Gynecol* 1951; **62**: 627–32

64 Morillo CA, Ellenbogen KA, Pava LF. Pathophysiologic basis for vasodepressor syncope. *Syncope* 1997; **15**: 233–49

65 Morita H, Vatner SF. Effects of hemorrhage on renal nerve activity in conscious dogs. *Circ Res* 1985; **57**: 788–93

66 Murray RH, Thompson LJ, Bowers JA, Albright CD.

Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *Am Heart J* 1968; **76**: 799–811

67 Nishikawa T, Anzai Y, Namiki A. Asystole during spinal anaesthesia after change from Trendelenburg to horizontal position. *Can J Anaesth* 1988; **35**: 406–8

68 Novak V, Honos G, Schondorf R. Is the heart 'empty' at syncope? *J Auton Nerv Syst* 1996; **60**: 83–92

69 Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat—a possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 1972; **85**: 164–73

70 Oberg B, White S. The role of vagal cardiac nerves and arterial baroreceptors in the circulatory adjustments to hemorrhage in the cat. *Acta Physiol Scand* 1970; **80**: 395–403

71 Olsson GL, Hallen B. Cardiac arrest during anaesthesia. A computer-aided study in 250,543 anaesthetics. *Acta Anaesthesiol Scand* 1988; **32**: 653–64

72 Paton JFR. Convergence properties of solitary tract neurones driven synaptically by cardiac vagal afferents in the mouse. *J Physiol* 1998; **508**: 237–52

73 Peters J, Kutkuhn B, Medert HA, Schlaghecke R, Schuttler J, Arndt JO. Sympathetic blockade by epidural anesthesia attenuates the cardiovascular response to severe hypoxemia. *Anesthesiology* 1990; **72**: 134–44

74 Quan KJ, Carlson MD, Thames MD. Mechanisms of heart rate and arterial blood pressure control: implications for the pathophysiology of neurocardiogenic syncope. *Pacing Clin Electrophysiol* 1997; **20**: 764–74

75 Rorsgaard S, Secher NH. Slowing of the heart during hypotension in major abdominal surgery. *Acta Anaesthesiol Scand* 1986; **30**: 507–10

76 Rosenberg JM, Wahr JA, Sung CH, Oh YS, Gilligan LJ. Coronary perfusion pressure during cardiopulmonary resuscitation after spinal anesthesia in dogs. *Anesth Analg* 1996; **82**: 84–7

77 Rutz K. Asystole on induction. *Anaesthesia* 1989; **44**: 698–9

78 Sander-Jensen K, Secher NH, Bie P, Warberg J, Schwartz TW. Vagal slowing of the heart during haemorrhage: observations from 20 consecutive hypotensive patients. *Br Med J* 1986; **292**: 364–6

79 Sander-Jensen K, Marving J, Secher NH *et al.* Does the decrease in heart rate prevent a detrimental decrease of the end-systolic volume during central hypvolaemia in man? *Angiology* 1990; **41**: 687–95

80 Scherrer U, Vissing S, Morgan BJ, Hanson P, Victor RG. Vasovagal syncope after infusion of a vasodilator in a heart transplant recipient. *New Engl J Med* 1990; **322**: 602–4

81 Scull TJ, Carli F. Cardiac arrest after Caesarean section under subarachnoid block. *Br J Anaesth* 1996; **77**: 274–6

82 Secher NH, Bie P. Bradycardia during reversible haemorrhagic shock—a forgotten observation? *Clin Physiol* 1985; **5**: 315–23

83 Shalev Y, Gal R, Tchou PJ *et al.* Echocardiographic demonstration of decreased left ventricular dimensions and vigorous myocardial contraction during syncope induced by head-up tilt. *J Am Coll Cardiol* 1991; **18**: 746–51

84 Sharpey-Schafer EP. Syncope. *Br Med J* 1956; **iii**: 506–9

85 Smith ML, Carlson MD, Thames MD. Nalaxone does not prevent vasovagal syncope during simulated orthostasis in humans. *J Auton Nerv Syst* 1993; **45**: 1–9

86 Somers VK, Abboud FM. Neurocardiogenic syncope. *Adv Intern Med* 1996; **41**: 399–435

87 Sprung J, Abdelmalak B, Schoenwald PK. Vasovagal cardiac arrest during the insertion of an epidural catheter and before the administration of epidural medication. *Anesth Analg* 1998; **86**: 1263–5

88 Stienstra R, Veering BT. Intrathecal drug spread: is it controllable? *Reg Anesth Pain Med* 1998; **23**: 347–51

89 Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Giani P. Proposed classification for tilt induced vasovagal syncope. *Eur J Card Pacing Electrophysiol* 1992; **3**: 180–3

90 Tarkkila P, Isola J. A regression model for identifying patients at high risk of hypotension, bradycardia and nausea during spinal anesthesia. *Acta Anaesthesiol Scand* 1992; **36**: 554–8

91 Tverskoy M, Shagal M, Finger J, Kissin I. Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. *J Clin Anesth* 1994; **6**: 487–90

92 Tverskoy M, Fleyshman G, Bachrak L, Ben-Shlomo I. Effect of bupivacaine-induced spinal block on the hypnotic requirement of propofol. *Anaesthesia* 1996; **51**: 652–3

93 Van Leeuwen AF, Evans RG, Ludbrook J. Haemodynamic responses to acute blood loss: new roles for the heart, brain and endogenous opioids. *Anaesth Intensive Care* 1989; **17**: 312–9

94 Van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci* 1991; **81**: 575–86

95 Van Lieshout JJ, Wieling W, Karemaker JM. Neural circulatory control in vasovagal syncope. *Pacing Clin Electrophysiol* 1997; **20**: 753–63

96 Verberne AJM, Guyenet PG. Medullary pathway of the Bezold–Jarisch reflex in the rat. *Am J Physiol* 1992; **263**: R1195–202

97 von Bezold A, Hirt L. Über die physiologischen Wirkungen des essigsauren Veratrins. *Untersuchungen aus dem physiologischen Laboratorium Wurzburg* 1867; **1**: 75–156

98 Wallin BG, Sundlof G. Sympathetic outflow to muscles during vasovagal syncope. *J Auton Nerv Syst* 1982; **6**: 287–91

99 Wasserstrum N. Nitroprusside in preeclampsia. Circulatory distress and paradoxical bradycardia. *Hypertension* 1991; **18**: 79–84.

100 Watkins EJ, Dresner M, Calow CE. Severe vasovagal attack during regional anaesthesia for Caesarean section. *Br J Anaesth* 2000; **84**: 118–20.

101 Ziegler MG, Echon C, Wilner KD, Specho P, Lake CR, McCutchen JA. Sympathetic nervous withdrawal in the vasodepressor (vasovagal) reaction. *J Auton Nerv Syst* 1986; **17**: 273–8.

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SHORT COMMUNICATIONS

Gastric residual volume in children: a study comparing efficiency of erythromycin and metoclopramide as prokinetic agents

T. F. Zatman*, J. E. Hall and M. Harmer

Department of Anaesthesia and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK

**Corresponding author*

Metoclopramide may be used to stimulate gastric emptying when anaesthetizing children for emergency operations. Unfortunately, metoclopramide is associated with extrapyramidal side effects. Erythromycin, a motilin receptor agonist, is a prokinetic agent but its use has been little investigated in children. This randomized double-blind study compared the effects of premedication with oral metoclopramide 0.15 mg kg^{-1} or erythromycin 1 mg kg^{-1} on gastric emptying in 80 children undergoing tonsillectomy. Pre-operative fluids, premedication and anaesthetic technique were standardized and gastric volume was measured with an orogastric tube. Post-operative nausea and vomiting was recorded. Metoclopramide and erythromycin produced similar gastric volumes (0.29 and 0.24 ml kg^{-1}) and there was no difference in post-operative vomiting. In the erythromycin group there were more patients with negative aspirates (45.9%) than in the metoclopramide group (35.1%), but the difference was not statistically significant. These results indicate that erythromycin may be as effective as metoclopramide as a prokinetic agent.

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In emergencies, it may be necessary to anaesthetize children who are not fully starved and consequently at risk of pulmonary aspiration. Children are recognized to be at increased risk of aspiration compared with adults,[1] [2] and Coté and colleagues[3] found that 76% of children had a gastric residual volume (GRV) of 0.4 ml kg^{-1} compared with 55% of adults.

Prokinetic agents such as metoclopramide can be used to reduce GRV. Metoclopramide is widely used as a prokinetic agent in adults and is licensed for premedication in children, but its use may be limited by its potential for producing extrapyramidal side effects. Erythromycin is an effective prokinetic agent in adults[4] but there is no work examining its use for premedication in children. This study compared the effects of erythromycin and metoclopramide on GRV in children undergoing tonsillectomy. An active comparator was used in the study as the combination of temazepam, pre-operative fluid intake and a tonsillectomy operation was felt to be potentially emetogenic. Oral metoclopramide 0.15 mg kg^{-1} was chosen as it has been shown previously to be effective. This dose produces peak plasma concentrations in 1.5–2.5 h[5] (the premedication interval used in our study), improves gastroesophageal reflux symptoms[6] and reduces nausea and vomiting in children undergoing tonsillectomy.[7]

Method and results

After Local Research Ethics Committee review and with written informed parental consent, 80 ASA grade I and II children of both sexes, aged 4–15 yr and undergoing tonsillectomy, were enrolled in the study. Exclusion criteria included a history of motion sickness, sleep apnoea, gastro-oesophageal reflux and other gastric pathology, and medication affecting gastric emptying.

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Table 1 Gastric residual volume and incidence of vomiting. Data are mean (SD), number (%) or median (interquartile range)

	Metoclopramide (n=37)	**Erythromycin** (n=37)	**Difference** (95% confidence interval)
Gastric residual volume, ml kg^{-1}	0.29 (0.5)	0.24 (0.3)	0.05 (–0.23 to 0.14)
No. with zero gastric aspirate (%)	13 (35.1)	17 (45.9)	
No. with gastric aspirate >0.4 ml kg^{-1} (%)	8 (21.6)	8 (21.6)	
No. of vomiting episodes	1 (0–3)	1 (0–3)	

The study was randomized and double-blind, and the children were allocated to two groups. Group 1 received oral metoclopramide 0.15 mg kg^{-1} and group 2 received oral erythromycin 1 mg kg^{-1} 2 h pre-operatively. Children also received temazepam syrup 0.3 mg kg^{-1} and extremely weak lemon squash 3 ml kg^{-1} at this time. Children were allowed clear fluids up to the time of premedication.

A standard anaesthetic was given involving pre-oxygenation, induction with thiopentone 5–6 mg kg^{-1} and morphine 0.1 mg kg^{-1} and intubation after succinylcholine 1 mg kg^{-1}. Anaesthesia was maintained with 1–2% halothane. Patients breathed spontaneously once the succinylcholine had worn off. After induction of anaesthesia, a blinded observer passed a multiport 16 g orogastric tube into the stomach. The tube position was checked by injecting 5 ml air down the tube and auscultating over the stomach. The orogastric tube was aspirated with a 20 ml syringe with the patient in supine, left and right lateral, Trendelenburg and reverse Trendelenburg positions. The tube was manipulated to various positions to ensure gastric emptying. The GRV was noted and the same volume of tap water returned to the stomach.

Nausea and vomiting was assessed for 18 h after operation using a numeric scale: 0=no nausea and vomiting; 1=nausea (assessed by asking children if they felt sick); 2=retching; 3=vomiting. Repeated incidents occurring within 15 min were classified as one episode. After operation, analgesia was provided by diclofenac (oral or rectal) or paracetamol. Pethidine was available.

Study size was determined using data from the work of Coté and colleagues.[3] His first group consisted of in-patients anaesthetized for the first time: this group of 12 showed a mean GRV of 0.86 ml kg^{-1} and a standard error of 0.2. This gives a calculated standard deviation of 0.7 and, if a decrease to a GRV of 0.4 ml kg^{-1} were considered to be significant, 80 patients would be necessary to show significance at the 0.05 level for a study with a power of 0.85.

Six children were withdrawn from the study: two did not drink all of their prokinetic agent, three did not drink their pre-operative drink and in one case a blinded anaesthetist was not available to pass the orogastric tube. There were no differences between the two groups in age range (4–15 yr) and mean (SD) weight [36 (16) and 31 (16) kg]. Male:female ratio was 12:25 in both groups. GRV was the same in both groups (Table 1). An empty stomach occurred more frequently in the erythromycin-treated than in the metoclopramide-treated children, but the difference was not significant. The incidence of vomiting did not differ between groups (Table 1). Retching occurred in four children in the metoclopramide group and in one in the erythromycin group; all of these eventually vomited. Nausea occurred in five children in each group; all of these eventually vomited. No child received pethidine and none had extrapyramidal side effects.

Comment

There was no significant difference between the remaining GRV after pretreatment with erythromycin or metoclopramide. There was no difference in the incidence of post-operative nausea and vomiting in the two groups. Twenty per cent of the patients in each group had a gastric volume greater than 0.4 ml kg^{-1}.

Erythromycin is a motilin receptor agonist. Erythromycin 2 mg kg^{-1} has been shown previously to cause less gastrointestinal effects in adults than therapeutic doses,[8] but in a pilot study in children[9] a high level of post-operative nausea and vomiting occurred at this dose. We considered this dose to be too high for peri-operative use in a group of children already at risk of vomiting; consequently a dose of 1 mg kg^{-1} was used.

Only one previous study has compared the effects of erythromycin and metoclopramide on gastric emptying. This was a randomized crossover study in diabetic adults.[10] Both drugs caused significant increases in gastric emptying, but it seemed more pronounced with erythromycin. The authors concluded that erythromycin could be used as an alternative to metoclopramide. The present study is the only work to date examining erythromycin as a pre-operative prokinetic agent in children, and it seems that the two treatments used in this study are similar in their effects on GRV. In emergencies, anaesthetists may wish to use erythromycin rather than metoclopramide, thus avoiding any potential for extrapyramidal side-effects. A dose of 1 mg kg^{-1} (lower than the therapeutic dose of 3–7 mg kg^{-1} in children over 2 yr) appears to avoid excessive gastrointestinal side-effects.

References

1 Kluger MT, Short TG. Aspiration during anaesthesia: a review of 133 cases from the Australian Anaesthetic Incident Monitoring Study (AIMS). *Anaesthesia* 1999; **54**: 19–26

2 Olsson GL, Hallen B, Hambraeus-Jonson K. Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. *Acta Anaesthesiol Scand* 1986; **30**: 84–92

3 Coté CJ, Goundsouzian NG, Liu LMP, Dedrick DF, Szfelbein S. Assessment of risk factors related to acid aspiration syndrome in paediatric patients—gastric pH and residual volume. *Anesthesiology* 1982; **56**: 70–2

4 Stern MA, Wolf DC. Erythromycin as a prokinetic agent: a prospective, randomized, controlled study of efficacy in naso-enteric tube placement. *Am J Gastroenterol* 1994; **89**: 2011–13

5 Kearns GL, Butler HL, Lane JK, Carchman SH, Wright GJ. Metoclopramide pharmacokinetics and pharmacodynamics in infants with gastroesophageal reflux. *J Ped Gastroenterol Nutr* 1988; **7**: 823–9.

6 Kearns GL, van den Anker JN, Reed MD, Blumer JL. Pharmacokinetics of metoclopramide in neonates. *J Clin Pharmacol* 1998; **38**: 122–8.

7 Ferrari LR, Donlon JV. Metoclopramide reduces the incidence of vomiting after tonsillectomy in children. *Anesth Anal* 1992; **75**: 351–4.

8 Tack J, Janssens J, Vantrappen G, et *al*. Effect of erythromycin on gastric motility in controls and in diabetic gastroparesis. *Gastroenterology* 1992; **103**: 72–9

9 Hall JE, Harmer M. Erythromycin as a prokinetic agent in children. *Anaesthesia* 1996; **51**: 503–4

10 Erbas T, Varoglu E, Erbas B, Tastekin G, Akalin S. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care* 1993; **16**: 1511–4

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Effect of intravenous magnesium on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers

S. Mikkelsen[1]*, J. Dirks[1], P. Fabricius[1], K. L. Petersen[2], M. C. Rowbotham[2 3] and J. B. Dahl[1]

[1]Laboratory of Pain Physiology, Department of Anaesthesiology, Copenhagen University Hospital, Herlev, Copenhagen, Denmark. [2]Department of Neurology and [3]Department of Anesthesiology, UCSF Pain Clinical Research Center, University of California, San Francisco, CA 94115, USA

**Corresponding author*

We investigated the effects of i.v. magnesium on secondary hyperalgesia following heat/capsaicin stimulation in human volunteers. Twenty-five volunteers were included in this double blind, randomized, crossover study. Sensitization was induced in the volunteers, who were then subjected to either i.v. saline or magnesium sulphate. No analgesic or antihyperalgesic effect could be demonstrated in sensitized skin during infusion of magnesium. In contrast, painfulness of thermal stimulation was increased in normal skin. These results suggest that i.v. magnesium has no important analgesic effects in clinically relevant doses.

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The *N*-methyl-D-aspartate (NMDA) receptor complex plays a significant role in a central sensitization, and has been implicated in mechanisms underlying both acute and chronic pain states.[1 2] NMDA receptor antagonists reduce central sensitization.[3] The NMDA receptor complex contains a magnesium ion block at resting membrane potential that prevents inward current flux of sodium and calcium ions.[1] The magnesium block is removed as part of the molecular sensitization process. We hypothesized that magnesium could re-establish channel block following activation and, thus, potentially reduce sensitization. Reversible cutaneous sensitization can be induced with an

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Table 1 VAS ratings, area of secondary hyperalgesia, heat pain detection thresholds and side effects. **P*=0.001, ***P*<0.002, ****P*<0.0001. (Median (quartiles)).

		Placebo	Magnesium 0.2 mg kg^{-1} + magnesium 0.2 mg kg^{-1} h^{-1}
VAS ratings during re-kindling (40°C for 5 min)	80 min	22 (8–33)	21 (10–31)
	120 min	7 (2–15)	6 (2–11)
Area of secondary hyperalgesia, pin-prick (cm^2)	Baseline	104 (81–130)	108 (88–135)
	80 min	81 (70–107)	83 (62–83)
	120 min	79 (63–98)	78 (63–107)
Area of secondary hyperalgesia, brush (cm^2)	Baseline	77 (61–114)	94 (72–110)
	80 min	59 (47–87)	59 (47–87)
	120 min	63 (41–83)	56 (41–82)
Heat pain detection threshold (°C) normal forearm	Baseline	44.0 (42.5–45.3)	44.0 (42.8–45.1)
	80 min	43.8 (42.1–44.7)	42.2 (40.4–43.3)*
	120 min	42.9 (41.7–44.2)	42.3 (40.9–43.2)*
Heat pain detection threshold (°C) sensitized forearm	Baseline	44.1 (42.9–46.3)	45.2 (43.2–45.9)
	80 min	42.6 (40.3–44.2)	43.4 (39.6–44.8)
	120 min	42.5 (41.6–43.8)	42.2 (41.3–44.4)
VAS ratings during long thermal stimulation (percentage of baseline value)	80 min	110 (91–138)	149 (122–192)**
	120 min	112 (94–138)	149 (126–207)**
Light-headedness		0 (0–0)	0.5 (0.25–1.0)***
Drowsiness		0 (0–0)	0.75 (0.25–1.125)***

intense noxious stimulation (thermal and/or chemical) creating a zone of primary hyperalgesia within the stimulated region. In the area surrounding the zone of primary hyperalgesia, there is a zone of secondary hyperalgesia.[4]

In this study, cutaneous sensitization was induced with a heat/capsaicin sensitization model, which combines thermal and chemical methods of nociceptor stimulation to produce stable and long-lasting hyperalgesia. Suppression of secondary hyperalgesia with opioid has been reliably demonstrated without skin injury using this model.[5] The aim of the study was to investigate the effects of i.v. magnesium on secondary hyperalgesia following heat/capsaicin sensitization, thermal thresholds and acute noxious thermal pain in healthy volunteers.

Methods and results

This two-session, crossover, double blind, randomized, placebo controlled study was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committee and the Danish National Board of Health. After providing informed written consent, 25 healthy male volunteers, aged 21–42 (mean 26) yr were included in the study. All subjects were familiarized with the experimental protocol on a separate screening day.

Heat/capsaicin sensitization was produced by heating the skin at the stimulation site to 45°C for 5 min. Immediately thereafter, the skin was covered with capsaicin cream (0.075% capsaicin, 7 g; Clay-Park Labs Inc, NY, USA) for 30 min. The sensitization was re-kindled twice throughout the infusion session with the thermode at 40°C for 5 min.

The areas of secondary hyperalgesia were measured by stimulating with a von Frey hair (21.5 g) and a foam brush along four linear paths arranged radially around the stimulation site. Stimulation was initiated outside the hyperalgesic area and continued towards the stimulation site until the subjects reported a definite change in perception. Area calculations were made using vector algorithm. Areas of secondary hyperalgesia were measured immediately after the initial sensitization, before drug infusion (baseline), and immediately after each re-kindling.

All thermal stimulations were performed using the Thermotest (Somedic A/B Sweden). The 25×50 mm thermode is a Peltier device that warms the skin surface at a linear rate (1.0°C s^{-1}) from a probe temperature of 32°C to a safety cut-off of 52°C. The heat pain detection thresholds (HPDT) were determined in the stimulation site and in normal skin before the induction of the heat/capsaicin sensitization (baseline), and after each re-kindling. The thermode was applied with a standardized pressure. By activating a button, the subjects indicated when the temperature of the thermode was first perceived as painful.

Another stimulation site was marked in normal skin on the non-dominant upper arm and in this site, subjects rated the pain associated with a 1 min long 45°C heat stimulation (long thermal stimulation, or LTS). Pain during LTS was determined before the induction of the heat/capsaicin sensitization (baseline), and after each re-kindling.

On the two infusion days, the subjects received either i.v. infusion of saline placebo or magnesium sulphate (bolus 0.2 mmol kg^{-1} over a period of 15 min, followed by 0.2 mmol kg^{-1} h^{-1}) for a total of 90 min. The study drugs were prepared according to a computer generated randomization list by an investigator who took no further part in the study. The subjects rated side-effects immediately after bolus infusion, and every 25 min on a scale from 0–3 (0=none, 1=slight, 2=moderate, 3=severe).

The procedures were performed according to the following schedule.

- −10 min: Heat pain detection threshold (HPDT), normal skin (baseline); pain rating (VAS) during LTS (baseline).

- 0 min: Induction of hyperalgesia: heat stimulation followed by capsaicin cream.
- 40 min: Area of secondary hyperalgesia for von Frey hair and brush stimulation (baseline).
- 45 min: Magnesium or placebo.
- 75–80 min: Re-kindling.
- 80 min: Area of secondary hyperalgesia for von Frey hair and brush stimulation; HPDT, sensitized and normal skin; VAS during LTS.
- 115–120 min: Re-kindling.
- 120 min: Area of secondary hyperalgesia for von Frey hair and brush stimulation; HPDT, sensitized and normal skin; VAS during LTS; end of magnesium/placebo infusion.

The sample size was based on a power calculation which showed that 25 volunteers were required to achieve 80% power to detect a difference of 20% in area of secondary hyperalgesia, with $\alpha=0.05$ (two-tailed).

Wilcoxon's test for paired data was used. Any significant P-values were corrected using Bonferroni's correction for repeated measurements. $P<0.05$ was considered statistically significant. Before statistical analyses, areas of secondary hyperalgesia, HPDT, and pain of LTS in individual volunteers were normalized in relation to the baseline values obtained before administration of the study drugs. The pain of LTS (45°C for 1 min) was calculated as area under the curve and then converted to VAS values (0–100).

Infusion of magnesium did not change the size of the areas of secondary hyperalgesia compared with placebo ($P>0.26$) (Table 1). In sensitized skin, HPDT did not differ regardless of treatment regimen ($P=0.88$ at 80 min, $P=0.97$ at 120 min). Heat pain detection thresholds were reduced in normal skin during magnesium infusion ($P=0.001$). Likewise, LTS was rated as more painful during infusion of magnesium than placebo ($P<0.002$). Infusion of magnesium caused significantly more lightheadedness ($P<0.0001$), and drowsiness ($P<0.0001$) than infusion of placebo.

Comment

One study has assessed the effect of i.v. magnesium administration in patients with chronic pain. Felsby and coworkers failed to demonstrate significant reductions in pain and area of allodynia in 10 patients with chronic neuropathic pain.[6]

In our study, i.v. magnesium had no effect on sensitization. Furthermore, magnesium had no analgesic effect on thermal stimulation in hyperalgesic skin. In contrast, magnesium decreased HPDT and increased the pain of LTS in normal skin. These results suggest that i.v. magnesium has no important analgesic effects in clinically relevant doses.

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References

1 Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: Wall PD and Melzack R, eds. *Textbook of Pain*. 4th Edn. Edinburgh: Churchill Livingstone, 1999; 165–83
2 Woolf CJ. Somatic pain – pathogenesis and prevention. *Br J Anaesth* 1995; **75**: 169–76
3 Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth* 1995; **75**: 193–200
4 Mikkelsen S, Ilkjær S, Brennum J, Borgbjerg FM, Dahl JB. The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. *Anesthesiology* 1999; **90**: 1539–45
5 Petersen KL, Jones B, Segredo V, Gaspar J, Dahl JB, Rowbotham MC. The effect of remifentanil on pain and secondary hyperalgesia associated with the heat/capsaicin model in healthy volunteers. *Anesthesiology* 2001: **94**: 15–20
6 Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. *Pain* 1996; **64**: 283–91

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Orally administered clonidine significantly reduces pain during injection of propofol[†]

T. Yoshikawa[1 2 3]*, Z. Wajima[2], A. Ogura[4], T. Inoue[2] and R. Ogawa[4]

[1]Department of Anaesthesia, Hakujikai Memorial Hospital, 5-11-1 Shikahama, Adachi-ku, Tokyo 123-0864, Japan. [2]Department of Anaesthesia, Chiba Hokusoh Hospital, Nippon Medical School, Chiba, Japan. [3]Department of Anaesthesiology, Tokyo Jikeikai Medical School, Tokyo, Japan. [4]Department of Anaesthesiology, Nippon Medical School, Tokyo, Japan

**Corresponding author*

We examined the analgesic effects of orally administered clonidine on pain induced by injection of propofol (Diprivan; 2,6-diisopropyl phenol). Female patients (n=81) were randomly allocated to one of two groups: oral clonidine (5.5 μg kg^{-1}) followed by i.v. propofol and a control group given placebo followed by i.v. propofol. The median pain score in the group receiving clonidine, using a four-point scale (0=no pain, 1=minimal pain, 2=moderate pain, 3=severe pain) was 1 (0–2), significantly lower than in the control group [2 (1–3), median (25–75 percentiles), P<0.001].

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Clonidine is an α_2 adrenergic agonist with analgesic and sedative properties. It also reduces the total requirement for propofol for general anaesthesia. Because of these characteristics, we examined the effects of clonidine premedication on pain associated with propofol injection.

Methods and results

The institutional ethics committee (Research Ethics Committee, Nippon Medical School) approved this study and each patient gave signed informed consent before enrolment. Eighty-one female patients (ASA physical status I or II, aged 30–60 yr) undergoing elective gynaecological laparotomy were allocated randomly to one of two groups. No patient received premedication apart from placebo or clonidine. Patients taking sedatives or analgesic agents and those with neurological or cardiovascular diseases were excluded from the study.

An 18-gauge Teflon cannula (Insyte-W Vialon E; Becton Dickinson, Franklin Lakes, NJ, USA) was inserted into the cephalic vein of the non-dominant hand, without infiltration of local anaesthetic, about 180 min before the induction of anaesthesia when the patient was still in the ward on the day of surgery. The cannula was used for i.v. infusion of Ringer's lactate solution.

Non-invasive systolic arterial blood pressure (ni-SBP), non-invasive diastolic arterial blood pressure (ni-DBP) and heart rate were recorded in the ward about 120 min before transferring the patient to the operating theatre and before administration of oral clonidine or placebo. Measurements were repeated in the operating theatre before induction of anaesthesia.

Patients in the clonidine group (n=41) were given powdered clonidine 5.5 μg kg^{-1} orally 120 min before induction of anaesthesia. Propofol 2.5 mg kg^{-1} was given into the cannula at induction of anaesthesia. Control patients (n=40) were given placebo (cornstarch 5.5 μg kg^{-1}) orally 120 min before induction of anaesthesia. Propofol was then administered as described for the clonidine group.

Propofol was kept in an incubator at 20–23°C until immediately before administration. It was infused through a three-way tap directly connected to the i.v. cannula, with the i.v. infusion line closed, using an electrically powered syringe pump (Graseby Anaesthesia Pump 3500; Graseby Medical, Hertfordshire, UK). The infusion rate was 3 mg kg^{-1} min^{-1} and the total amount infused was 2.5 mg kg^{-1}. Before administration of propofol, the patient was requested to rate immediately any sensation of pain during injection as either none (0), mild (1), moderate (2) or severe (3), similar to the method used in previous studies.[1 2 3]

[†] This work was carried out at Chiba Hokusoh Hospital, Nippon Medical School, 1715 Kamakasi Inba-mura, Inba-gun, Chiba 270–1694, Japan.

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Table 1 Characteristics and pain scores of clonidine-treated and control groups. The number of patients with each pain score is shown. Pain score in each group is given as median and 25th and 75th percentiles. ni-SBP=non-invasive systolic arterial blood pressure; ni-DBP=non-invasive diastolic arterial blood pressure. Continuous variables are expressed as mean (SD); n.s.=not significant. *$P<0.05$ compared with values measured in the ward

	Clonidine group	**Control group**	***P***
No. of patients	41	40	
Pain score			
0	11	0	
1	17	6	
2	13	15	
3	0	19	
Median (25th, 75th percentiles)	1 (0, 2)	2 (1, 3)	<0.001
Age (yr)	44.5 (31–59)	43.8 (32–55)	n.s.
Height (cm)	156 (5.1)	156 (4.9)	n.s.
Weight (kg)	54 (8.3)	54 (7.2)	n.s.
ASA grades I, II	20, 21	23, 17	n.s.

	Clonidine group			**Control group**		
	ni-SBP (mm Hg)	**ni-DBP (mm Hg)**	**Heart rate (beats min^{-1})**	**ni-SBP (mm Hg)**	**ni-DBP (mm Hg)**	**Heart rate (beats min^{-1})**
Ward	122 (17.4)	73 (11.0)	74 (13.5)	120 (16.2)	73 (11.5)	72 (10.4)
Theatre	112 (16.9)	66 (9.5)*	65 (12.4)*	128 (22.2)	74 (10.8)	75 (14.7)

A blinded anaesthetist recorded the reported degree of pain. The maximum degree of pain reported before the patient fell asleep was recorded as the pain score (pain score) for that patient. We also recorded the interval before pain was experienced. If there was no pain, this interval was recorded as 50 s, representing the total time required for injecting the propofol.

After induction of anaesthesia, the lungs were ventilated mechanically with 30–50% oxygen in air through an endotracheal tube, in combination with epidural anaesthesia and continuous i.v. propofol.

Power calculation indicated that recruitment of 40 patients in each group would be sufficient to demonstrate a reduction of pain score of 1 at a level of significance of $P=0.05$ and power of 99.3%. Statistical analysis was carried out using SPSS version 10.0 and SamplePower J version 1.0 (SPSS, Chicago, IL, USA), on a Toshiba DynaBook Satellite 2520 computer running the Microsoft J Windows 98 operating system.

Differences in continuous variables between groups were statistically evaluated with the unpaired *t*-test, ASA status with the χ^2 test and pain score with the Mann–Whitney *U*-test. The relationship between pain score and time to pain was analysed with Spearman's rank correction coefficient, excluding patients with a pain score of 0 because there were no patients with a pain score of 0 in the control group. A *P* value of <0.05 was regarded as significant.

There were no significant differences in patient characteristics between the control and clonidine groups. Median pain score in the clonidine group was 1 (0–2), significantly lower than the score of 2 (1–3) in control patients ($P<0.001$) (Table 1).

There was no significant relationship between the pain score and time to pain. In the clonidine-treated group, ni-DBP and heart rate were significantly lower in the operating theatre than in the ward ($P<0.05$). In the control group, there were no significant changes in ni-SBP, ni-DBP or heart rate (Table 1). None of the patients developed profound hypotension or bradycardia that required treatment (data not shown).

Comments

The incidence of injection pain on propofol injection is 25–100%.[2] The mechanism responsible for the pain is unknown, but activation of the kinin cascade system has been suggested.[4] Several approaches have been used to reduce injection pain. Among these, the most popular is the use of lidocaine either by mixing lidocaine with propofol or by pretreatment with a bolus injection of lidocaine. The former technique seems to be more effective than the latter.[4]

Previous studies have demonstrated that oral clonidine administered before anaesthesia increases the analgesic effects of opioids after operation[5 6] and reduces anaesthetic[7] and/or opioid requirement[8 9] during the peri-operative period, and that clonidine attenuates the haemodynamic responses to noxious stimuli such as tracheal intubation.[8 10] Because of these beneficial properties, clonidine is a useful premedication. Our results demonstrate the efficacy of oral clonidine for pain on injection of propofol.

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References

1 Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: a comparison of lidocaine with alfentanil. *Anesth Analg* 1996; **82**: 469–71

2 Yokota S, Komatsu T, Komura Y, *et al.* Pretreatment with topical 60% lidocaine tape reduces pain on injection of propofol. *Anesth Analg* 1997; **85**: 672–74

3 Iwama H, Nakane M, Ohmori S, *et al.* Nafamostat mesilate, a kallikrein inhibitor, prevents pain on injection with propofol. *Br J Anaesth* 1998; **81**: 963–4

4 Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–4

5 Goyagi T, Nishikawa T. Oral clonidine premedication enhances the quality of postoperative analgesia by intrathecal morphine. *Anesth Analg* 1996; **82**: 1192–6

6 Park J, Forrest J, Kolesar R, *et al.* Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth* 1996; **43**: 900–6

7 Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg* 1982; **61**: 741–5

8 Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42

9 Flacke JW, Bloor BC, Flacke WE, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9

10 Lauruto CE, Baughman VL, Becker CL, De Silva TW, Carranza CJ. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses to laryngoscopy. *Can J Anaesth* 1991; **3**: 186–93

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Efficacy of varying concentrations of hyaluronidase in peribulbar anaesthesia

C. Mantovani[1], A. E. Bryant[2] and G. Nicholson[2]*

[1]Department of Anaesthesia, Bromley Hospital, Cromwell Avenue, Bromley, Kent BR2 9AJ, UK.
[2]Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK
**Corresponding author*

We have compared the efficacy of adding varying concentrations of hyaluronidase to a standard mixture of 2% lidocaine and 1% ropivacaine to provide peribulbar anaesthesia for cataract surgery. We used (i) the time to adequate anaesthesia for surgery and (ii) ocular and eyelid movement scores at 8 min after block as clinical endpoints. Ninety patients were randomly allocated to receive 7–10 ml of equal volumes of 2% lidocaine and 1% ropivacaine without hyaluronidase or with hyaluronidase 15 IU ml^{-1}or 150 IU ml^{-1}. Median time at which the block was adequate for surgery was 6 min in all groups (interquartile range 4–12 min). Median eyelid movement scores were similar in all groups, but the ocular movement scores at 8 min were significantly lower in the group which received hyaluronidase 150 IU ml^{-1} than in the group not given hyaluronidase ($P<0.03$). There were no differences between groups in the incidence of minor complications. A high concentration of hyaluronidase resulted in a statistically significantly lower ocular movement score at 8 min; the clinical relevance of this finding is uncertain.

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Keywords: anaesthetic techniques, regional, peribulbar; enzymes, hyaluronidase

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Regional anaesthesia is the technique of choice for the vast majority of patients undergoing cataract surgery. Peribulbar anaesthesia is considered safer than injections inside the extraocular muscle cone, especially when non-ophthalmologists perform the block. A mixture of bupivacaine and lidocaine is the most frequently used local anaesthetic combination, with hyaluronidase and epinephrine frequently added in various concentrations to this mixture. Hyaluronidase hydrolyses the C1–C4 bonds between glucosamine and glucuronic acid in ground substance,

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thus promoting spread of the anaesthetic through the tissue. The proposed advantages of using hyaluronidase include enhanced speed of onset and improved operating conditions.

There are, however, conflicting data about the advantages of hyaluronidase in peribulbar anaesthesia. Concentrations as low as 7.5 IU ml^{-1} have been reported to be effective,[1] whereas other studies found no benefit at a higher concentration of 150 IU ml^{-1}.[2] We found in a previous study[3] that excellent operating conditions were achieved in a median time of 8 min using the low concentration of 15 IU ml^{-1}, as recommended by the *British National Formulary*,[4] added to equal volumes of 2% lidocaine and 0.75% bupivacaine and to 1% ropivacaine. Concerns have been expressed about the use of hyaluronidase as it involves injecting a foreign protein into the orbit with the risk of sensitization and allergic reactions if re-injected. As many patients need cataract surgery twice, it is pertinent to ascertain if the addition of hyaluronidase to the anaesthetic mixture is necessary. We compared, therefore, the efficacy of anaesthesia obtained with the standard concentration of 15 IU ml^{-1} hyaluronidase, no hyaluronidase and a high concentration of 150 IU ml^{-1}.

Table 1 Median (interquartile range) ocular and eyelid movement scores and time to anaesthesia. *$P<0.03$ for difference between no hyaluronidase and hyaluronidase 150 IU ml^{-1}

		Hyaluronidase	
	No hyaluronidase	**15 IU ml^{-1}**	**150 IU ml^{-1}**
Ocular movement			
2 min	6 (2–8)	5 (2–8)	4 (2–6)
4 min	4 (0–6)	4 (0–6)	2 (0–4)
6 min	3 (0–5)	2 (0–6)	0 (0–2)
8 min	1 (0–4)	0 (0–4)	0 (0–1)*
Eyelid movement			
2 min	1 (1–2)	1 (0–2)	1 (0–2)
4 min	1 (0–1)	1 (0–1)	0 (0–1)
6 min	0 (0–1)	0 (0–1)	0 (0–0)
8 min	0 (0–1)	0 (0–1)	0 (0–0)

Methods and results

Following hospital Ethics Committee approval and written informed consent, we studied 90 patients presenting for cataract surgery under local anaesthesia. Patients were excluded if they were unwilling to take part, if there were communication or language problems, or if there was a history of allergy to amide-type local anaesthetic agents. Patients were randomly allocated to one of three groups using a random number table. All patients received an equal volume of 1% ropivacaine and 2% lidocaine. In group 1 no hyaluronidase was added to the anaesthetic mixture and in groups 2 and 3 hyaluronidase was added to give a final concentration of 15 and 150 IU ml^{-1}, respectively. The anaesthetic solution was warmed to body temperature.

Patients were not fasted and did not receive any premedication, perioperative sedation or supplemental oxygen. On arrival in the induction room, baseline eyelid and globe movements were assessed. Topical anaesthesia of the conjunctiva and cornea was achieved by administering two or three drops of 0.4% oxybuprocaine. Standard monitoring was commenced and i.v. access established. Peribulbar block was carried out, by one of two consultant anaesthetists, via a single transcutaneous inferolateral injection using a 25-gauge, 25 mm needle directed backwards in a sagittal plane, tangentially to the globe and parallel to the floor of the orbit. The bevel of the needle faced the globe. Following test aspiration, 8 ml of the local anaesthetic mixture was injected over 30–40 s (range 7–10 ml to allow for very heavy or very frail patients). Different volumes of local anaesthetic were used depending on the degree of filling of the orbit observed during the injection and the rate of onset of ptosis during injection. An additional facial nerve block was not required, as akinesia of the orbicularis oculi was achieved by a peribulbar block. Manual compression and gentle massage of the eyeball were performed, after which a Visitec intraocular pressure reducer, inflated to 40 mm Hg, was applied between scoring. Eyelid and ocular movements were assessed at 2 min intervals with a scoring system described previously.[3] Scoring was carried out by an independent, trained observer, who was blinded as to which anaesthetic mixture the patient had received.

Ocular movements were scored for each direction of gaze in a superior, inferior, medial and lateral direction with a maximum score for each direction of three points and therefore a possible maximum total of 12 points. Ocular and eyelid movements were assessed at 2, 4, 6 and 8 and 10 min until the block was considered adequate for surgery. If the block was inadequate after 10 min, supplementary anaesthesia was provided with a further injection of up to 5 ml of the test solution, by the same technique. The time to adequate surgical anaesthesia was noted as well as the need for supplementary anaesthesia. It was assumed that, once motor block had been achieved, adequate sensory block was already present, as this precedes motor block. Complications during or after injection were recorded and patients were specifically questioned about pain during insertion of the block, or during surgery.

Outcome criteria were defined as the time needed to reach adequate block to start the operation and the difference in median ocular and eyelid movement scores at 8 min; differences between groups were analysed by Kruskal–Wallis one-way analysis of variance (ANOVA) for non-parametric data. *Post hoc* analysis was undertaken with the Mann–Whitney test; a P-value of ≤ 0.03 was considered statistically significant. The number of patients who reached an ocular movement score of 0 or 1, the need for further injections, delays to the start of surgery and the occurrence of complications were compared using χ^2 or Fischer's exact test, as appropriate. Statistical analysis was carried out using SPSS 8.0 package for Windows 95.

The three groups were similar in age, sex and mean axial length of the globe. There were 30 patients in group 1, 31 in group 2 and 29 in group 3 because one patient was mistakenly assigned to the wrong group. The mean (range) ages were 73 (46–91) yr in group 1, 71 (54–88) yr in group 2 and 74 (51–91) yr in group 3. The male:female ratio was 10:20 in group 1, 15:16 in group 2 and 12:17 in group 3. The mean (SD) axial length was 23.6 (1.4) mm in group 1, 24.1 (1.7) mm in group 2 and 23.4 (1.3) mm in group 3.

The median time at which patients were adequately anaesthetized was 7 min in group 1, 6 min in group 2 and 4 min in group 3 (P=0.089). Median ocular movement scores at 8 min were significantly lower in group 3 than in group 1 (P=0.014) which was the other predefined endpoint (Table 1). Twenty-three patients in group 3 achieved ocular movement scores of $\leq$1, compared with 16 in group 1 and 18 in group 2 (P=0.088). There was no significant difference between groups in terms of requirements for supplementary anaesthesia: 10 patients in group 1, nine in group 2 and four in group 3 required additional anaesthesia. Four patients in group 1, two in group 2 and one in group 3 sustained minor complications.

Comment

We have shown that hyaluronidase at a concentration of 150 IU ml^{-1} resulted in a significantly lower ocular movement score at 8 min and this was associated with a non-significant improvement in speed of onset of the block.

Hyaluronidase is of ovine origin and acts by hydrolysing the C1–C4 bonds between glucosamine and glucuronic acid. It depolymerizes the glycosaminoglycan-rich ground substance which normally obstructs intercellular diffusion. It has been suggested that hyaluronidase increases the permeability of the fibrous septa which compartmentalize the orbital contents, thereby enhancing the uniform spread of local anaesthetic.[5]

Studies have produced widely conflicting results on the possible advantages of using hyaluronidase, but these differences may arise partly from a number of confounding variables, including the choice of anaesthetic solution, injection site and techniques, as well as the pH of the anaesthetic solution. Morsman and Holden found improved anaesthetic conditions with hyaluronidase at a concentration of 50 IU ml^{-1}.[5] Sarvela and Nikki observed similar improvements with a concentration of 7.5 IU ml^{-1}; no additional benefit was found when the concentration was doubled.[1] Two studies found that hyaluronidase at a concentration of 10–15 IU ml^{-1} improved the efficacy of peribulbar block when the anaesthetic solution was alkalinized to a pH of 6.7.[6 7] Conversely, Lewis and colleagues observed a faster onset with pH-adjusted anaesthetic solution, but no difference in time to complete anaesthesia between patient groups, all of whom received hyaluronidase 15 IU ml^{-1}, and indeed increased requirements for supplementary anaesthesia in the pH-adjusted group.[8] In contrast, other more recent studies have observed no benefit when using hyaluronidase at concentrations of 25, 50 or 150 IU ml^{-1},[2 9 10] and improved speed of onset of block only when used in a concentration of 300 IU ml^{-1}.[11]

Our standard practice is to inject 8 ml of local anaesthetic mixture; rarely, very small or very large patients received a slightly smaller or greater volume. Nevertheless, it is unlikely that the differences in speed of onset of block found in this study are the result of differences in dose of local anaesthetic. In our study, an experienced consultant anaesthetist performed all blocks, and this probably resulted in the short time to adequate anaesthesia. In this situation, the use of hyaluronidase confers no practical advantages and we cannot recommend it. However, when anaesthetic trainees are learning peribulbar anaesthetic techniques, hyaluronidase may be useful in compensating for a less expert technique.

References

1 Sarvela J, Nikki P. Hyaluronidase improves regional ophthalmic anaesthesia with etidocaine. *Can J Anaesth* 1992; **39**: 920–4

2 Bowman RJC, Newman DK, Richardson EC, Callear AB, Flanagan DW. Is hyaluronidase helpful for peribulbar anaesthesia? *Eye* 1997; **11**: 385–8

3 Nicholson G, Sutton B, Hall GM. Comparison of 1% ropivacaine with 0.75% bupivacaine and lidocaine for peribulbar anaesthesia. *Br J Anaesth* 2000; **84**: 89–91

4 *British National Formulary* 2000; **39**: 10.3.1, p. 469. London: British Medical Association and Royal Pharmaceutical Society of Great Britain.

5 Morsman CD, Holden R. The effects of adrenaline, hyaluronidase and age on peribulbar anaesthesia. *Eye* 1992; **6**: 290–2

6 Zahl K, Jordan A, McGroarty J, Gotta AW. pH-adjusted bupivacaine and hyaluronidase for peribulbar block. *Anesthesiology* 1990; **72**: 230–32

7 Roberts JE, MacLeod BA, Hollands RH. Improved peribulbar anaesthesia with alkalinisation and hyaluronidase. *Can J Anaesth* 1993; **40**: 835–8

8 Lewis P, Hamilton RC, Loken RG, Maltby JR, Strunin L. Comparison of plain with pH-adjusted bupivacaine with hyaluronidase for peribulbar block. *Can J Anaesth* 1992; **39**: 555–8

9 Prosser DP, Rodney GE, Mian T, Jones HM, Khan MY. Re-evaluation of hyaluronidase in peribulbar anaesthesia. *Br J Ophthal* 1996; **80**: 827–30

10 Crawford M, Kerr WJ. The effect of hyaluronidase on peribulbar block. *Anaesthesia* 1994; **49**: 907–87

11 Dempsey GA, Barrett PJ, Kirby IJ. Hyaluronidase and peribulbar block. *Br J Anaesth* 1997; **78**: 671–4

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Midazolam *versus* propofol for reducing contractility of fatigued canine diaphragm

Y. Fujii* and H. Toyooka

Department of Anaesthesiology, University of Tsukuba Institute of Clinical Medicine, 2-1-1 Amakubo, Tsukuba City, Ibaraki, Japan

**Corresponding author*

The effects of midazolam and propofol on the contractility of fatigued canine diaphragm were examined. Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz applied for 30 min. After fatigue had been induced, group I (n=10) received no study drug, group II (n=10) was given a propofol infusion (0.1 mg kg^{-1} loading dose plus 1.5 mg kg^{-1} h^{-1} maintenance dose) and group III (n=10) was given a midazolam infusion (0.1 mg kg^{-1} loading dose plus 0.1 mg kg^{-1} h^{-1} maintenance dose). Diaphragmatic contractility was assessed by measuring transdiaphragmatic pressure (P_{di}). After the fatigue-inducing period in each group, P_{di} at low-frequency (20 Hz) stimulation was lower than the baseline values (P<0.05), whereas no change in P_{di} at high-frequency (100 Hz) stimulation was observed. In group II, P_{di} at 20 Hz stimulation was lower than fatigued values (P<0.05); P_{di} at 100 Hz stimulation did not change. In group III, P_{di} at both stimulation frequencies was lower than fatigued values (P<0.05). Compared with group I, P_{di} at 20 Hz stimulation was lower than fatigued values (P<0.05) during administration of the study drug in groups II and III. The decrease in P_{di} was greater in group III than in group II (P<0.05). In conclusion, midazolam compared with propofol is associated with an inhibitory effect on contractility in the fatigued canine diaphragm.

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Fatigue of the respiratory muscles, especially diaphragm, may cause respiratory failure.[1] Like volatile anaesthetics, propofol reduces diaphragmatic contractility.[2] Midazolam and propofol are widely used for equivalent sedation.[3] However, little is known about the effects of these drugs on the contractility of fatigued diaphragm. The purpose of this study was to examine the efficacy of midazolam compared with propofol on the contractility of fatigued canine diaphragm.

Methods and results

Institutional approval for the study was obtained from the animal care and uses committee of the University of Tsukuba School of Medicine. Thirty healthy adult mongrel dogs, weighing 10–15 kg (mean (SD) 12.6 (1.6) kg), were anaesthetized and mechanically ventilated. Animals were prepared as described previously.[2] Anaesthesia was maintained with pentobarbital 2 mg kg^{-1} h^{-1} i.v., supplemented as necessary to sustain adquate anaesthesia. Muscle relaxants and analgesics were not used. Tracheas were intubated. Ventilation was mechanically controlled with a mixture of oxygen and air (FI_{O_2} 0.4) to maintain Pa_{O_2}, Pa_{CO_2} and pH_a within normal ranges. The femoral artery (for monitoring arterial blood pressure) and vein (for administering the study drugs, propofol and midazolam) were cannulated. Transdiaphragmatic pressure (P_{di}) was measured by means of two thin-walled latex balloons, one positioned in the stomach and the other in the middle third of the oesophagus. Balloons were connected to a differential pressure transducer and an amplifier. Both phrenic nerves were exposed at the neck and the stimulating electrodes were placed around them. Supramaximal electrical stimuli (10–15 V) of 0.1 ms duration were applied for 2 s at low or high frequency (20 and 100 Hz, respectively) with an electrical stimulator. The isometric contractility of the diaphragm was evaluated by measuring the maximal P_{di} after airway occlusion at functional residual capacity. The

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Table 1 Changes in hemodynamics, P_{di} (cm H_2O) and $\%E_{di}$. Values are mean (SD). MAP=mean arterial pressure, P_{di}=transdiaphragmatic pressure, $E_{di\text{-}cru}$=integrated electrical activity of the crural part of diaphragm, $E_{di\text{-}cost}$=integrated electrical activity of the costal part of diaphragm. Group I received no study drug, group II received propofol 1.5 mg kg^{-1} h^{-1} and group III received midazolam 0.1 mg kg^{-1} h^{-1}. [a]Significantly different from baseline (P<0.05); [b]significantly different from fatigued (P<0.05); [c]significantly different from group I (P<0.05); [d]significantly different from group II (P<0.05)

Variable	Group	Baseline	Fatigued	Treatment
Haemodynamics				
Heart rate (beats min^{-1})	I	142 (12)	141 (11)	142 (10)
	II	143 (11)	141 (12)	131 (11)[a,b,c]
	III	143 (10)	143 (11)	132 (12)[a,b,c]
MAP (mm Hg)	I	126 (10)	125 (11)	126 (9)
	II	125 (11)	125 (13)	118 (10)[a,b,c]
	III	127 (10)	127 (9)	117 (11)[a,b,c]
P_{di} (cm H_2O)				
20 Hz stimulation	I	15.6 (1.6)	12.1 (2.0)[a]	12.2 (1.8)[a]
	II	15.4 (1.5)	12.0 (1.8)[a]	10.1 (1.6)[a,b,c]
	III	15.5 (1.9)	11.9 (1.6)	8.8 (1.5)[a,b,c,d]
100 Hz stimulation	I	20.9 (2.0)	21.0 (1.8)	20.8 (1.9)
	II	21.1 (1.8)	20.9 (1.8)	21.0 (2.0)
	III	20.9 (2.1)	20.6 (1.8)	18.5 (2.0)[a,b,c,d]
$\%E_{di\text{-}cru}$				
20 Hz stimulation	I	100.0 (0.0)	98.9 (3.2)	98.9 (3.2)
	II	100.0 (0.0)	98.9 (3.2)	100.0 (6.8)
	III	100.0 (0.0)	98.9 (3.2)	98.9 (5.8)
100 Hz stimulation	I	100.0 (0.0)	99.4 (1.8)	100.0 (2.7)
	II	100.0 (0.0)	99.4 (1.8)	99.4 (3.2)
	III	100.0 (0.0)	98.8 (2.3)	89.9 (7.3)[a,b,c,d]
$\%E_{di\text{-}cost}$				
20 Hz stimulation	I	100.0 (0.0)	98.9 (3.2)	99.5 (3.6)
	II	100.0 (0.0)	98.9 (3.2)	98.9 (3.2)
	III	100.0 (0.0)	99.1 (2.8)	99.1 (5.1)
100 Hz stimulation	I	100.0 (0.0)	99.4 (1.8)	99.0 (3.9)
	II	100.0 (0.0)	99.4 (1.8)	99.4 (1.8)
	III	100.0 (0.0)	99.4 (1.8)	88.0 (5.9)[a,b,c,d]

electrical activity of the diaphragm was recorded by two pairs of electrodes and was rectified and integrated with a leaky integrator with a time constant of 0.1 s. This was regarded as the integrated electrical activity of the crural ($E_{di\text{-}cru}$) and costal ($E_{di\text{-}cost}$) parts of the diaphragm.

Dogs were randomly divided into three groups of 10. After measuring baseline values of P_{di}, $E_{di\text{-}cru}$, $E_{di\text{-}cost}$ and haemodynamic variables, including heart rate and mean arterial pressure (MAP), in each group, diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30 min at a frequency of 20 Hz, an entire cycle of 4 s and a duty cycle of 0.5 (i.e. low-frequency fatigue).[4] After the fatigue-inducing period, group II was given a bolus injection of propofol 0.1 mg kg^{-1} followed by a continuous infusion (1.5 mg kg^{-1} h^{-1}) i.v. with an electrical infusion pump for 60 min; group III received i.v. midazolam (0.1 mg kg^{-1} loading dose plus 0.1 mg kg^{-1} h^{-1} maintenance dose) continuously with an infusion pump for 60 min. After administration of the study drug, P_{di}, $E_{di\text{-}cru}$, $E_{di\text{-}cost}$ and haemodynamic variables were measured. The doses used in the current study were based on the observation that a subhypnotic dose (1.5 mg kg^{-1} h^{-1}) of propofol and a sedative dose (0.1 mg kg^{-1} h^{-1}) of midazolam were widely used for equivalent sedation.[3 5] In group I, only maintenance fluids were administered, and the same measurements were performed. The changes in $E_{di\text{-}cru}$ and $E_{di\text{-}cost}$ ($\%E_{di\text{-}cru}$ and $\%E_{di\text{-}cost}$, respectively) from baseline were measured. At the end of the experiment, animals were killed with an overdose of pentobarbital.

Values are expressed as mean (SD). Statistical analysis was performed by ANOVA with Bonferroni correction for multiple comparison and Student's t-test, as appropriate. P values of <0.05 were considered significant.

No differences in baseline variables were observed among the groups. In groups II and III, heart rate and MAP decreased below baseline (P<0.05) during administration of the study drug. After the fatigue-inducing period, P_{di} at low-frequency (20 Hz) stimulation was lower than baseline (P<0.05) and P_{di} at high-frequency (100-Hz) stimulation did not change in each group. In group II, P_{di} at 20 Hz stimulation was lower than fatigued values (P<0.05); P_{di} at 100 Hz stimulation did not change. In group III, P_{di} at both stimuli was lower than fatigued values (P<0.05). The decrease in P_{di} was greater in group III than in group II (P<0.05). In group III, both $E_{di\text{-}cru}$ and $E_{di\text{-}cost}$ at 100 Hz stimulation during midazolam administration were less than baseline values (P<0.05) (Table 1).

Comment

Low-frequency fatigue is of particular clinical importance because the spontaneous, natural rate of the phrenic nerve firing is mainly within the low-frequency ranges (i.e. 5–30 Hz).[6] In this study, therefore, we examined the effects of midazolam and propofol on the contractility of fatigued diaphragm induced by 20 Hz stimulation (i.e. low-frequency fatigue) were examined. The results of group I, in which P_{di} and E_{di} were observed without an infusion of propofol or midazolam, showed that P_{di} at both stimulation frequencies had no tendency to recover in the fatigued diaphragm and that E_{di} did not change at either stimulation frequency. This was in agreement with a previous study by us.[7]

In a preliminary study, we examined the effects of propofol on contractility in the non-fatigued diaphragm. With an infusion of propofol at a subhypnotic dose (1.5 mg kg^{-1} h^{-1}), P_{di} at 20 Hz stimulation was lower than baseline; P_{di} at 100 Hz stimulation and E_{di} did not change.[3] In group II, P_{di} at 20 Hz stimulation was lower than fatigued values ($P<0.05$); P_{di} at 100 Hz stimulation and E_{di} did not change. These results suggest that propofol may decrease the contractility of both fatigued and non-fatigued diaphragms. The exact mechanism by which propofol decreases the contractility of the diaphragm is unknown. However, these phenomena during propofol administration are similar to the characteristics of low-frequency fatigue, which is also related to impaired coupling of excitation and contraction.[4 8] Therefore, it is possible that an inhibitory effect of propofol on diaphragmatic muscle function may be related to an impediment of excitation–contraction coupling.

In group III, midazolam reduced P_{di} at both stimulation frequencies compared with fatigued values ($P<0.05$), and $E_{di\text{-}cru}$ and $E_{di\text{-}cost}$ at 100 Hz stimulation during midazolam administration were less than those obtained in the baseline period ($P<0.05$). The precise mechanism by which midazolam reduces the contractility of fatigued diaphragm with a reduction of electromyographic activity (as assessed by E_{di}) is not known. Selective loss of force at low-frequency stimulation is closely related to the impairment of excitation–contraction coupling,[8] whereas selective loss of force and electromyographic activity at high-frequency stimulation indicates the failure of neuromuscular transmission.[9 10] Therefore, reductions in P_{di} at low- (20 Hz) and high-frequency (100 Hz) stimulation and in E_{di} at high-frequency (100-Hz) stimulation may result from impairment of excitation–contraction coupling and failure of neuromuscular transmission.

In conclusion, we have shown that midazolam, compared with propofol, reduces P_{di} at both stimulation frequencies in fatigued diaphragm ($P<0.05$), suggesting that midazolam causes more contractile inhibition.

References

1 Macklem PT, Roussos C. Respiratory muscle fatigue: a cause of respiratory failure? *Clin Sci Mol Med* 1977; **53**: 419–22

2 Fujii Y, Hoshi T, Takahashi S, Toyooka H. Propofol decreases diaphragmatic contractility in dogs. *Anesth Analg* 1999; **89**: 1557–60

3 Reves JG, Fragen RJ, Vinik R, Greenblatt DJ. Midazolam. Pharmacology and uses. *Anesthesiology* 1985; **62**: 310–24

4 Grassino A, Goldman MD, Mead J, Sears TA. Mechanics of the human diaphragm during voluntary contraction: statics. *J Appl Physiol* 1978; **44**: 829–39

5 Smith I, White PF, Nathanson M, Gouldson R. Propofol. An update on its clinical use. *Anesthesiology* 1994; **81**: 1005–43

6 Roussos C, Macklem PT. The respiratory muscles. *New Engl J Med* 1982; **307**: 786–97

7 Fujii Y, Takahashi S, Toyooka H. The effects of milrinone and its mechanism in fatigued diaphragm in dogs. *Anesth Analg* 1998; **87**: 1077–82

8 Moxham J, Wiles CM, Newham D, Edwards RHT. Contractile function and fatigue of the respiratory muscles in man. In: Porter R, Whelan J, eds. *Human Muscle Fatigue*. Ciba Foundation Symposium, No. 82. London: Pitman Medical, 1981; 197–205

9 Edwards RHT. Physiological analysis of skeletal muscle weakness and fatigue. *Clin Sci Mol Med* 1987; **54**: 463–70

10 Jones DA, Bigland-Ritchie B, Edwards RHT. Excitation frequency and muscle fatigue: mechanical responses during voluntary and stimulated contraction. *Exp Neurol* 1979; **64**: 401–13

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CASE REPORTS

Xenon anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome[†]

J. Hofland*, **I. Gültuna and R. Tenbrinck**

Department of Anaesthesiology, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands

**Corresponding author: Department of Anaesthesiology, Erasmus Medical Centre Rotterdam Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands*

There are few reports on anaesthesia for patients with Eisenmenger's syndrome requiring non-cardiac surgery and none of the use of xenon. We describe the use of xenon with a closed-circuit system in a patient with Eisenmenger's syndrome having a laparoscopic cholecystectomy.

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Eisenmenger's syndrome describes patients with an anomalous circulation leading to obliterative pulmonary vascular disease, where reversal of a left-to-right shunt has occurred.[1]

More patients with congenital heart disease now survive into adulthood, including patients with Eisenmenger's complex, a non-restrictive ventricular septal defect, with increased pulmonary vascular resistance that relieves the left ventricle of excessive volume overload and not increasing afterload on the right ventricle.[2] The longer these patients survive, the more likely they are to need non-cardiac surgery, such as a cholecystectomy.[3] In patients undergoing such procedures, peri-operative cardiac morbidity is a leading cause of peri-operative death.[3] Patients with Eisenmenger's syndrome are at particular high risk, with mortality reaching 30%, partly because they are vulnerable to changes in haemodynamics during the procedure.[3]

Xenon anaesthesia can be useful when cardiovascular stability is needed.[4 5] We therefore decided to use xenon for anaesthesia in a patient with Eisenmenger's syndrome presenting for laparoscopic cholecystectomy.

Case report

A 51-yr-old woman (1.51 m, 66 kg) with Down's syndrome was scheduled for a laparoscopic cholecystectomy because she had suffered from typical cholelithiasis for 6 months. Preoperative evaluation of the patient showed severe cyanosis, peripheral oxygen saturation (Sp_{O_2}) 86%, with clubbing of the fingers, secondary polycythaemia (haemoglobin 187 g l^{-1}, haematocrit 0.55) and oxygen requirement during exercise. She took diclofenac 50 mg orally for gall bladder pain. Arterial blood pressure was 140/80 mm Hg and heart rate 76 beats min^{-1}. Heart sounds included a loud second sound, an ejection click and a grade II diastolic murmur, loudest in the left parasternal region. The lungs were clear and hepatomegaly was not present. Echocardiography showed dilation of the pulmonary artery trunk with its branches, dilation of the right atrium, a hypertrophied right ventricle and mild tricuspid valve regurgitation. Peak pulmonary valve velocity was 1.2 m s^{-1} and there was pulmonary valve regurgitation with a velocity of 4.3 m s^{-1}. Pulmonary hypertension was caused by a perimembranous ventricular septal defect. Systolic and diastolic function of the left ventricle was normal, with an ejection fraction of 65%. Dilation of the left atrium was caused by two regurgitant jets from the mitral valve.

Written consent to use xenon was given by the patient's legal representative. The evening before the operation, the patient was premedicated with oxazepam 10 mg and ranitidine 150 mg. On the day of operation she took her

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[†] Part of this work was presented as a poster at the First Rotterdam Congress on Xenon Anesthesia, June 17, 2000, Rotterdam, The Netherlands.

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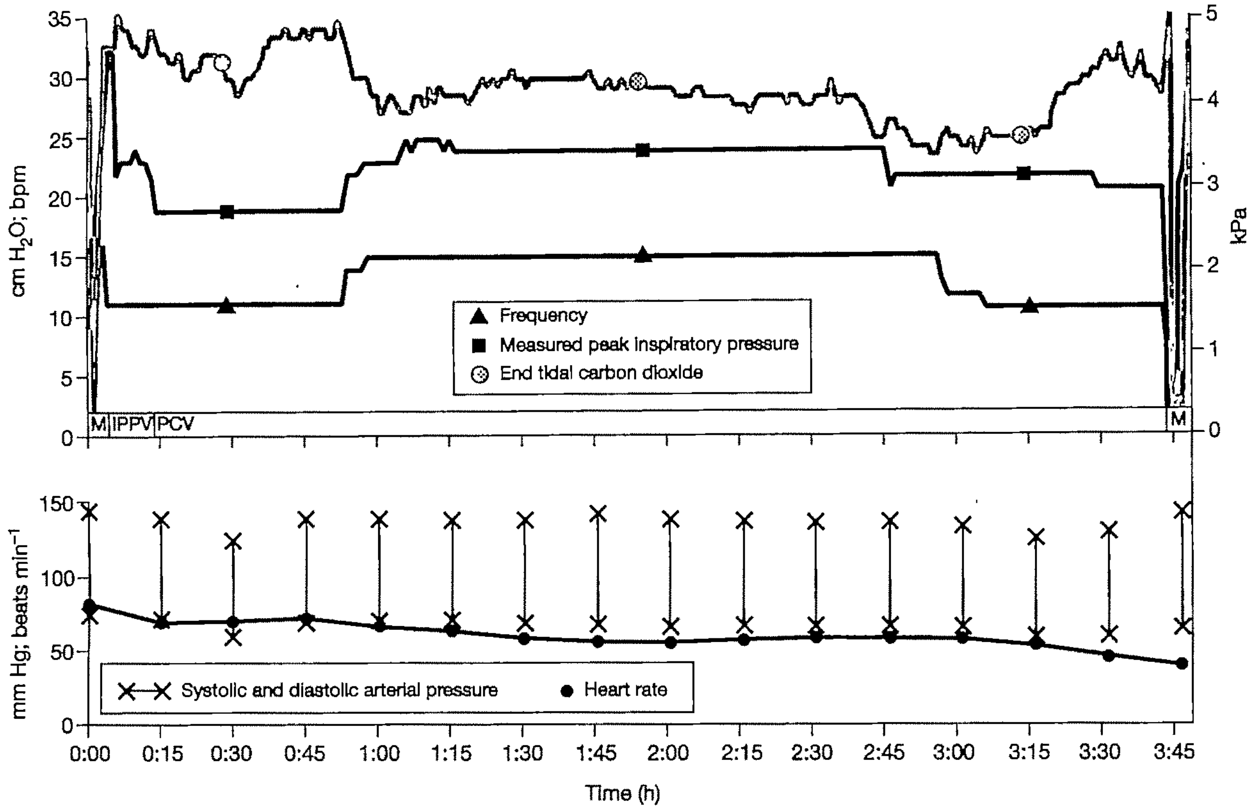

Fig 1 Systolic and diastolic arterial pressure (mm Hg), heart rate (beats min^{-1}), ventilator settings, frequency (b.p.m.), measured peak inspiratory pressure (cm H_2O) and end-tidal carbon dioxide (kPa). M=manual ventilation or spontaneous breathing; IPPV=intermittent positive-pressure ventilation; PCV=pressure-controlled ventilation.

routine analgesic medication, to which ranitidine 150 mg and lorazepam 1 mg were added.

In the operating room, basic anaesthetic monitoring was started. Before induction of anaesthesia, antibiotic prophylaxis for endocarditis (amoxicillin 1 g and gentamicin 240 mg) were given i.v. The patient was given 100% oxygen for 3 min for washout of nitrogen and at the same time phenylephrine infusion was started at 1.5 μg kg^{-1} min^{-1}. After sufentanil 25 μg and ketamine 40 mg i.v., a radial artery was cannulated. Induction of anaesthesia was continued with a further dose of ketamine 60 mg i.v. and then *cis*-atracurium 13 mg i.v. After tracheal intubation, the patient was connected to and ventilated with a closed-circuit anaesthetic machine (Physio, Haarlem, The Netherlands), using intermittent positive-pressure ventilation with settings of $F\text{I}_{O_2}$ 1.0, frequency 1 litre min^{-1}, tidal volume 540 ml, positive end-expiratory pressure (PEEP) 5 cm H_2O and I/E ratio 1:1.2 (Fig. 1). A cannula was placed in an internal jugular vein and a nasogastric tube was inserted along with a 5 MHz multi plane transoesophageal echoprobe (MPTE) probe for peroperative transoesophageal echocardiography (Sonotron Vingmed CFM 800, Vingmedsound Als, Horten, Norway). Xenon was then added to give a concentration of 60% (Fig. 2). The ventilator was reset to pressure-controlled ventilation with settings of PEEP 5 cm H_2O, inspiratory pressure change 13 cm H_2O, $F\text{I}_{O_2}$ 0.30, frequency 1 litre min^{-1} and I/E ratio 1:1 (Fig. 1). Two additional doses of sufentanil were given i.v., 15 μg at the start of surgery and 10 μg just establishing the pneumoperitoneum. Muscle relaxation was monitored continuously with a nerve stimulator (TOF-Guard; Biometer, Odense, Denmark). Additional doses of i.v. *cis*-atracurium were given as needed. When the inspired xenon fraction reached 60%, the phenylephrine infusion was decreased to 1.0 μg kg^{-1} min^{-1} because blood pressure and heart rate remained stable (Fig. 1), decreased to 0.5 μg kg^{-1} min^{-1} 10 min later and stopped 30 min after the pneumoperitoneum had been established. Ringer's lactate was given by infusion. Because the patient had not had any oral intake, we gave 22 ml kg^{-1} in the first hour then 7.5 ml kg^{-1} h^{-1}. In the first hour we also gave 500 ml of a colloid. Cardiac filling status was monitored by transoesophageal echocardiography using the transgastric short-axis mid-papillary view, and shunting through the perimembranous ventricular septal defect was assessed with a four-chamber view.

The increased end-tidal carbon dioxide ($F\text{E}_{CO_2}$) after pneumoperitoneum had been countered by increasing the inflation pressure to 18 cm H_2O, peak pressure 23 cm H_2O and the frequency to 15 b.p.m. (Fig. 1). Arterial blood samples were analysed immediately in an ABL 505 and an OSM 3 haemoxymeter (both from Radiometer, Copenhagen, Denmark) for blood gases and haemoglobin

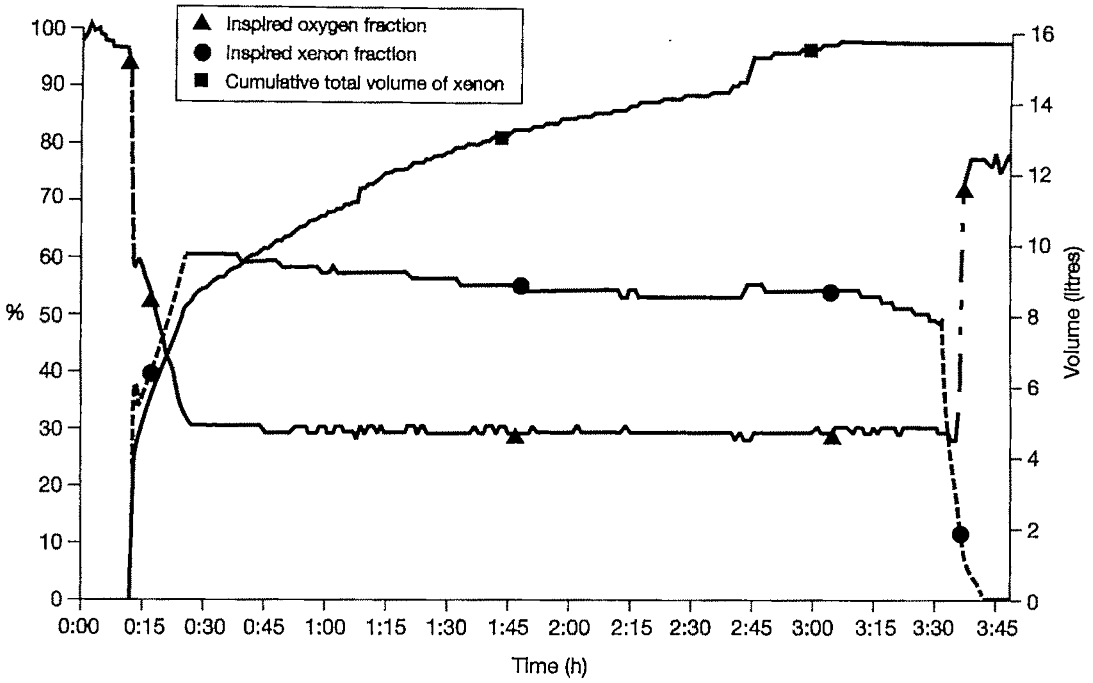

Fig 2 Inspired oxygen fraction (%), inspired xenon fraction (%) and cumulative total volume of xenon (litres).

Table 1 Results of blood sample analysis and results for $F_{I_{O_2}}$, $S_{p_{O_2}}$ and $F_{E_{CO_2}}$. $F_{I_{O_2}}$=inspired oxygen fraction; $S_{p_{O_2}}$=peripheral oxygen saturation; $F_{E_{CO_2}}$=end-tidal carbon dioxide; Hb=haemoglobin; P_{CO_2}=partial pressure of carbon dioxide; P_{O_2}=partial pressure of oxygen; HCO_3^- = bicarbonate ion; BE=base excess; S_{O_2}=blood gas oxygen saturation. Arterial samples were taken from the radial artery and the venous sample was drawn from the internal jugular vein. ND=no data available. 1=after induction of anaesthesia; 2=after starting pneumoperitoneum; 3=in the recovery room.

Variable	Arterial (1)	Arterial (2)	Venous (2)	Arterial (3)
$F_{I_{O_2}}$	1.0	0.30	0.30	0.21
$S_{p_{O_2}}$ (%)	99	93	93	88
$F_{E_{CO_2}}$ (kPa)	4.7	4.7	4.7	ND
Hb (g litre^{-1})	176	155	148	166
pH	7.39	7.34	7.32	7.35
P_{CO_2} (kPa)	5.9	6.4	6.7	6.6
P_{O_2} (kPa)	62.1	9.5	5.3	6.8
HCO_3^- (mmol litre^{-1})	26.2	25.1	25.2	26.1
BE (mmol litre^{-1})	1.3	−0.9	−1.1	0.3
S_{O_2} (%)	100	93	71	84

(Table 1) respectively. Intra-abdominal pressure was maintained at less than 16 mm Hg. At the end of the laparoscopy the patient was placed in the Trendelenburg position for a short time to allow surgical access. Surgery was uneventful. Morphine 7 mg i.v. was given 30 min before the operation finished. After the release of the pneumoperitoneum, inflation pressure was reduced to 15 cm H_2O and frequency to 11 b.p.m. (Fig. 1). Neuromuscular block was not antagonized. The patient breathed spontaneously 7 min after washout of xenon started, and 5 min later the trachea was extubated. After 90 min in the recovery room the patient was discharged to a normal surgical ward with additional oxygen 2 litre min^{-1} via a nasal tube for 24 h. Paracetamol 1 g three times a day orally, with additional morphine intramuscularly if required (only a single dose of 5 mg was given), was prescribed to maintain post-operative analgesia. The patient made an uneventful recovery and was discharged home 4 days after operation.

Discussion

The cornerstone of the anaesthetic management of patients with Eisenmenger's syndrome is maintenance of the preoperative systemic vascular resistance (SVR).[6]

Xenon anaesthesia is particularly useful when cardiovascular stability needs to be maintained.[4] Before xenon is used, nitrogen must be washed out of the lungs. High-flow pure oxygen over a period of at least 5 min is recommended.[4] We gave 100% oxygen before and after endotracheal intubation (Fig. 2).

Ketamine has been recommended as the drug of choice for induction because it has little effect on pulmonary and systemic vascular resistance, whereas thiopentone and propofol decrease SVR.[7] For the same reason, atracurium and vecuronium have been recommended for muscle relaxation.[8] Pretreatment with phenylephrine to prevent changes in SVR is also recommended, although it may cause similar vasoconstriction in both pulmonary and systemic circulations and therefore have only little effect on the shunt direction.[7]

We gave phenylephrine during induction with sufentanil, ketamine and *cis*-atracurium. The cardiovascular stability provided by xenon allowed the initial infusion rate to be reduced, after xenon had been washed in, to its preset level. Because carbon dioxide insufflation into the peritoneal cavity could cause hypotension, we stopped the infusion 30 min after pneumoperitoneum had been initiated; no resulting haemodynamic changes were observed (Fig. 1).

This haemodynamic stability forms a sharp contrast to an earlier case report in which anaesthesia had been maintained with 1–2% enflurane after induction with etomidate, which induced a 40% decrease in mean arterial pressure.[6] In patients with Eisenmenger's syndrome, halothane, enflurane and isoflurane can all cause systemic hypotension because of a varying combination of myocardial depression and vasodilation.[7] Although propofol was not used for maintenance of anaesthesia in these latter studies, similar haemodynamic changes might occur because low-dose propofol (1–2 mg kg^{-1}) gives anaesthetic conditions similar to an opioid–volatile anaesthetic technique with enflurane in cardiac patients before cardiopulmonary bypass.[9]

Patients with Eisenmenger's syndrome have lost the ability to adapt to sudden changes in haemodynamics because of a fixed pulmonary disease.[3] The value of a pulmonary artery flotation catheter in management is controversial.[3 6 7] Oesophageal echocardiography allowed non-invasive monitoring of cardiac filling, monitoring of the shunt and monitoring of possible gas embolism during gas insufflation of the peritoneal cavity. Monitoring of intra-arterial pressure, allowing continuous measurement and blood gas determination, is generally accepted.[3 6 7]

Low inflation pressures, with maintenance of Pa_{CO_2} to prevent deleterious effects on the intracardiac shunt during mechanical ventilation[10], were obtained by the use of pressure-controlled ventilation and frequency adjustment during pneumoperitoneum (Fig. 1).

Doses of muscle relaxant should be kept to the minimum compatible with performance of the surgical procedure.[10] In this way, no reversal agent of neuromuscular blockade was necessary at the end of the procedure in the present case, so that undesirable effects on the cardiovascular system were avoided.[10] The low blood gas partition coefficient of xenon (0.115) permits more rapid recovery than when nitrous oxide is used,[5 11] and early tracheal extubation, recommended for patients with Eisenmenger's syndrome, can be achieved.[6] Because morphine was given before the end of surgery, the recovery time of our patient was prolonged. However, 7 min after washout of xenon started, achieved by increasing $F\text{I}_{\text{O}_2}$ to 80%, the patient breathed spontaneously and 5 min later she was extubated uneventfully (Fig. 1).

Although xenon is a rare and expensive gas, a closed-circuit system can reduce the cost of xenon anaesthesia.[4] When xenon is given by this method, approximately 6 litres is taken up in the first hour in an average adult, and 9–15 litres in the first 2 h of xenon administration.[4] Since 1997 we have used the PhysioFlex closed-circuit anaesthetic machine for xenon administration. The total xenon uptake in our patient was 15.6 litres after 3 h and in the first hour 11.6 litres was taken up (Fig. 2). This means that longer anaesthetic procedures are more cost-effective. The surgical procedure also interferes with the absorption of xenon.[12] About an extra litre of xenon was absorbed by our patient when the operating table was returned from the Trendelenburg position to the normal position with simultaneous release of the pneumoperitoneum (Fig. 2; 2:45 h). Xenon anaesthesia for this patient cost an extra $150. Avoiding one day in the intensive care unit saves about $350. A previous study reported that patients with Eisenmenger's syndrome who underwent relatively minor procedures were monitored post-operatively on a normal ward, but overnight observation in an intensive care unit is usually recommended.[3 7] A patient undergoing laparoscopic cholecystectomy was scheduled pre-operatively for a one-night post-operative stay in the intensive care unit.[6]

This case shows that cardiovascular stability can be obtained by the use of xenon anaesthesia in a patient with Eisenmenger's syndrome. It also shows that avoiding admission to the intensive care unit by the use of xenon can be cost-effective if a closed-circuit system such as the PhysioFlex is used and the duration of the surgical procedure is long enough. Monitoring by transoesophageal echocardiography during anaesthesia should be considered for patients with Eisenmenger's syndrome. Xenon anaesthesia proved satisfactory for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome.

Acknowledgement

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References

1 Wood P. The Eisenmenger syndrome, or pulmonary hypertension with reversed central shunt. *Br Med J* 1958; **2**: 701–9, 755–62

2 Perloff JK. Congenital heart disease in adults. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 4th Edn. Philadelphia: W. B. Saunders, 1992; 971

3 Ammash NM, Connolly HM, Abel MD, Warnes CA. Noncardiac surgery in Eisenmenger syndrome. *J Am Coll Cardiol* 1999; **33**: 222–7

4 Lynch C III, Baum J, Tenbrinck R. Xenon anesthesia. *Anesthesiology* 2000; **92**: 865–70

5 Lachmann B, Armbruster S, Schairer W, *et al.* Safety and efficacy

of xenon in routine use as an inhalation anaesthetic. *Lancet* 1990; **335**: 1413–5

6 Sammut MS, Paes ML. Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome. *Br J Anaesth* 1997; **79**: 810–12

7 Lyons B, Motherway C, Casey W, Doherty P. The anaesthetic management of the child with Eisenmenger's syndrome. *Can J Anaesth* 1995; **42**: 904–9

8 Foster JMG, Jones RM. The anaesthetic management of the Eisenmenger syndrome. *Ann R Coll Surg Engl* 1984; **66**: 353–5

9 Hall RI, Murphy JT, Moffitt EA, Landymore R, Pollak PT, Poole L. A comparison of the myocardial metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. *Can J Anaesth* 1991; **38**: 996–1004

10 Lumley J, Whitwam JG, Morgan M. General anesthesia in the presence of Eisenmenger's syndrome. *Anesth Analg* 1977; **56**: 543–7

11 Goto T, Suwa K, Uezono S, Ichinose F, Uchyiama M, Morita S. The blood-gas partition coefficient of xenon may be lower than generally accepted. *Br J Anaesth* 1998; **80**: 255–6

12 Tenbrinck R, Reyle Hahn M, Gültuna I *et al.* The first clinical experiences with xenon. *Int Anesthesiol Clin* in press.

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Respiratory failure after tracheal extubation in a patient with halo frame cervical spine immobilization—rescue therapy using the Combitube airway

M. Mercer

Department of Anaesthesia, Frenchay Hospital, Bristol BS16 1LE, UK

A 78-yr-old man, with halo frame cervical spine immobilization, suffered rapid respiratory deterioration after tracheal extubation in the intensive care unit. Control of the airway was difficult as bag-valve-mask ventilation was ineffective, tracheal intubation was known to be difficult from management of a previous episode of respiratory failure on the ward, and laryngeal mask insertion proved impossible. Rescue therapy using a Combitube airway is described and discussed.

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In the most recent guidelines from the European Resuscitation Council, oral tracheal intubation remains the method of choice to secure the emergency airway.[1] The Combitube airway (Kendall Ltd, Gosport, UK) is included in these guidelines as an adjunct, along with the laryngeal mask airway (LMA)[1]†, if tracheal intubation fails.

The Combitube (Fig. 1) is a twin lumen device that is inserted blindly into the oropharynx. Each lumen is named to correspond to the position it will be in when used for ventilation of the lungs. One lumen (the 'tracheal' lumen) opens distally, the second (the 'oesophageal' lumen) opens at more proximally placed side ports. A large inflatable cuff (85–100 ml) is sited proximal to the side ports, whilst a small inflatable cuff (12–15 ml) is sited distally. It is usually positioned with the smaller cuff in the oesophagus,[2 3] such that ventilation of the lungs occurs through the proximal side ports, with the larger cuff sealing the hypopharynx.

This case describes two episodes of emergency airway management in the same patient who had halo frame cervical spine immobilization in place. The first occurred during the patient's initial respiratory decompensation when ventilation was secured with a LMA. The second episode occurred following tracheal extubation towards the end of the patient's stay in the intensive care unit, when rescue

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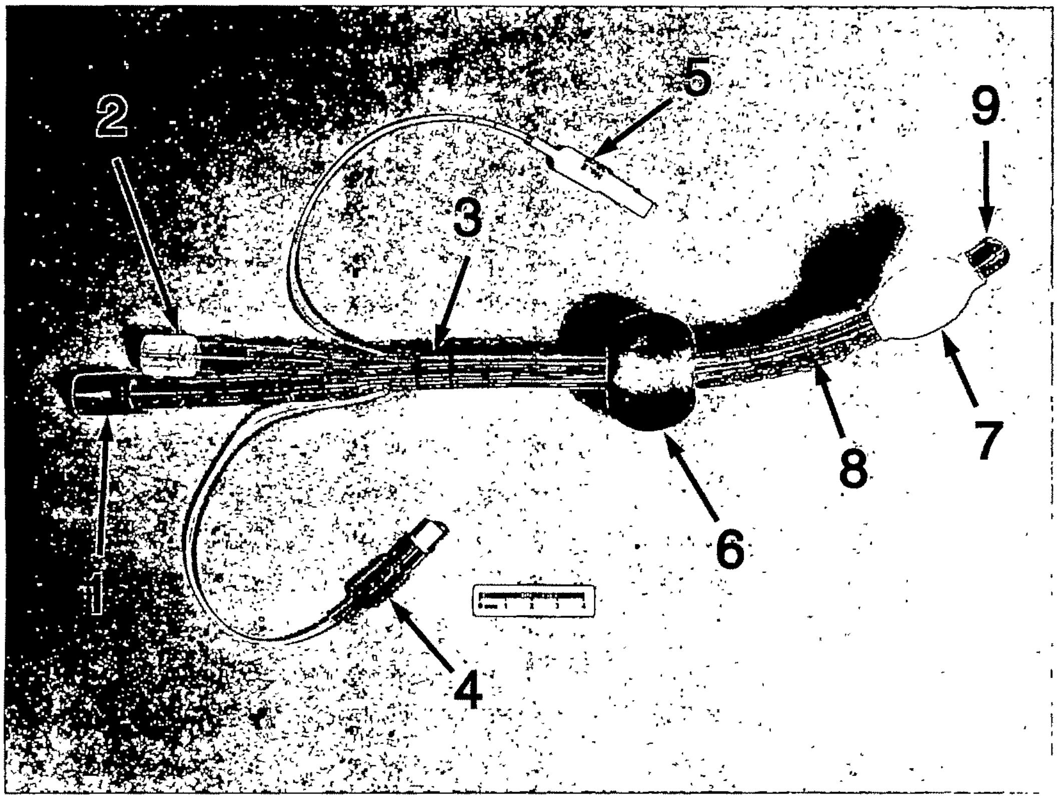

Fig 1 The Combitube airway (photograph). 1, Oesophageal lumen; 2, tracheal lumen; 3, ring markings to coincide with teeth; 4, pilot balloon for proximal, large cuff; 5, pilot balloon for distal, small cuff; 6, large cuff; 7, small cuff; 8, side port openings of oesophageal (proximal) lumen; 9, opening of tracheal (distal) lumen.

therapy using the Combitube airway was lifesaving as all other techniques had failed.

Case report

A 78-yr-old man, weighing 76 kg, was referred to the regional neurosurgical centre (day 1) for care of a transverse fracture through the base of the odontoid peg (Fig. 2), which was accompanied by posterior displacement of the first cervical vertebra (C1) and the obontoid peg in relation to the second cervical vertebra (C2). He had suffered neck pain for 3 days after tripping over a cobble stone and falling forward onto his forehead, so causing an extension injury at the craniovertebral junction. During this time, his wife reported his oral intake of food and fluids had been poor. A lateral cervical spine x-ray requested at this stage by his general practitioner revealed the injury. Halo frame cervical spine immobilization was applied at the referring hospital, comprising a thoracic vest supporting a halo ring attached to the skull.

His past medical history was complicated. In 1982, he had undergone Starr-Edwards aortic valve replacement and had been fully anticoagulated with warfarin ever since. He had breathlessness at rest, and was chronically in atrial fibrillation and biventricular cardiac failure. An echocardiogram in 1998 had revealed a dilated, severely impaired left ventricle with moderate mitral regurgitation.

His medications were warfarin 5 mg daily, amiodarone 100 mg daily, bumetanide 2 mg daily, enalapril 20 mg daily, bendrofluazide 2.5 mg daily and temazepam 10–20 mg at night. He was a non-smoker.

On examination at the referring hospital, he was dehydrated, with an arterial pressure of 100/60 mm Hg, and pulse of 80 beats min^{-1} in atrial fibrillation. There was a mitral regurgitant murmur and the jugular venous pressure was 5 cm. Neurological examination was normal. INR was 4.4 (normal range 0.9–1.3), plasma urea 31.8 mmol litre^{-1}, and creatinine 380 mmol litre^{-1}.

At the neurosurgical centre the warfarin was stopped, and cautious i.v. rehydration commenced. An early decision was taken to adopt conservative, non-surgical, therapy for this man in view of his debilitating intercurrent morbidities.

On day 2, x-rays revealed the cervical alignment to be inadequate warranting further manipulation of the craniocervical junction into flexion of approximately 5–10 degrees in the halo frame, such that the odontoid peg and body of C1 would be moved anteriorly on C2. The patient was kept nil-by-mouth for 6 h. On the ward during the procedure, he became increasingly tachypnoeic with peripheral oxygen saturation decreasing to 60% despite administration of a

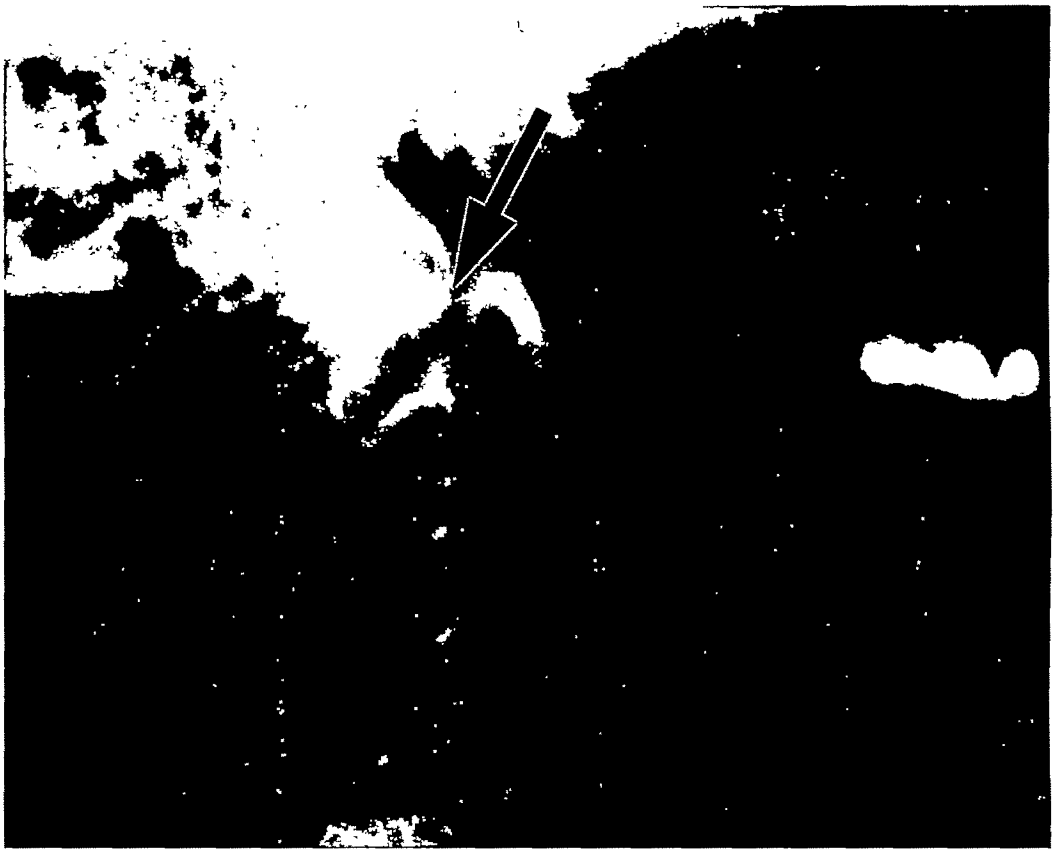

Fig 2 Lateral cervical spine x-ray with arrow indicating fracture through the base of the odontoid peg.

high flow of oxygen by Hudson mask. This was followed by a deterioration in conscious level and obstruction of the airway.

Anaesthetic assistance was urgently requested and the ward emergency airway trolley immediately made available. Bag-valve-mask ventilation was found to be impossible. A good mask to face seal was possible, but the airway remained obstructed despite the use of oro- and nasopharyngeal airways, and oral suctioning. The patient was noted to have unrestricted mouth opening and full dentition. I.v. propofol 20 mg followed by succinylcholine 100 mg was given. With a Macintosh 3 blade, the epiglottis was not visible (Cormack and Lehane grade 4) but nothing was seen that could have caused airway obstruction. As other laryngoscope blades were not contained in the emergency trolley, the procedure was abandoned. A size 4 LMA was then successfully placed at the first attempt. With restoration of the airway, and bag-valve ventilation of the lungs through the LMA with 100% oxygen, peripheral resaturation to 100% occurred. Cardiac output was not lost at any stage. I.v. vecuronium 10 mg was given, and manual ventilation continued. The patient was transferred to the intensive care unit for artificial ventilation of the lungs. Sedation was maintained with a 1% propofol i.v. infusion at 10–20 ml h^{-1}. Fibreoptic visualization of the vocal cords and trachea was possible through the LMA, enabling a size 6-cuffed tracheal tube to be passed over the fibrescope to secure the airway. This tube was then removed over a gum elastic bougie and replaced by a size 9-cuffed tracheal tube. At this stage, the patient was seen to move all four limbs.

The morning of the following day (day 3), further fluoroscopic reduction of the cervical spine involving 5–10 degrees of craniocervical flexion in the halo frame, was undertaken in the operating theatre. Again, all limbs were seen to move after the procedure.

The patient was now breathing spontaneously on the Siemens Servo 300 ventilator at a rate of 18 bpm with triggered pressure support/positive end-expiratory pressure assistance of 12/5 cm H_2O, generating tidal volumes of 7–8 ml kg^{-1}. With an inspired oxygen concentration of 40%, peripheral oxygen saturation was 99% and arterial carbon dioxide partial pressures less than 6.6 kPa. He was obeying commands with open eyes, and was coughing on the tracheal tube. Arterial pressure was 140/80 mm Hg. Following pre-oxygenation for 3 min, and oral and tracheal suctioning, he was extubated and given high flow oxygen by reservoir bag mask. Tachypnoea immediately followed, with peripheral oxygen saturations decreasing to 70%. His conscious level deteriorated. As before, bag-valve-mask ventilation was unsuccessful as the airway was obstructed. This was unrelieved by oral or by nasal airways, and suctioning. Tracheal intubation was not attempted in view

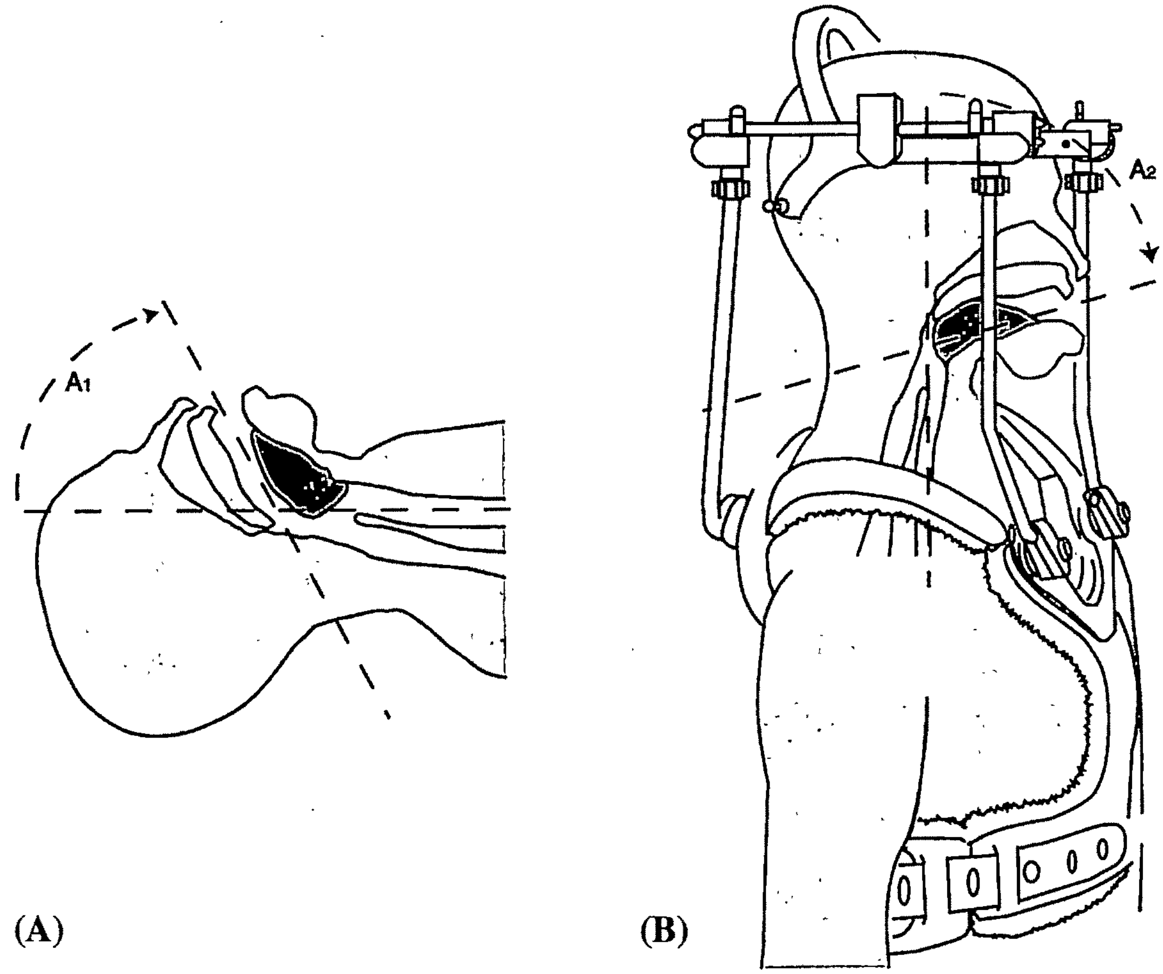

Fig 3 (A) Patent airway of supine patient before craniocervical flexion (diagrammatic). Halo frame not shown. (B) After second episode of craniocervical flexion. Obstructed airway of extubated patient sat up in bed (diagrammatic). Halo frame shown. Angle A2 is greater than A1 in (A).

of the previous difficulties, and unlikelihood of rapid control of the airway. Despite the gag response now being absent, attempts to insert a size 4 and 3 LMA, with and without digital guidance, were on this occasion unsuccessful. The LMAs would not pass beyond the oropharynx. Further peripheral desaturation to 60% occurred accompanied by a decrease in invasive arterial systolic pressure to 60 mm Hg, and electrocardiography showing a broad complex tachycardia of 140 beats min^{-1}. Peripheral i.v. methoxamine 20 mg was quickly followed by epinephrine 1 mg as the systolic pressure decreased further. Respiratory effort was now diminishing. At this stage, a small adult size Combitube was inserted without difficulty into the oesophagus and the cuffs inflated to the manufacturer's guidelines (small cuff 12 ml, large cuff 85 ml). Manual ventilation of the lungs was immediately possible using a high-flow oxygen, bag-valve system through the proximal side ported, oesophageal lumen of the Combitube. This was confirmed by bilateral chest expansion, auscultation of the lungs and an improvement in the peripheral saturation to 98%. After control of the airway and breathing, infusions of epinephrine 0.15 μg kg^{-1} min^{-1} and norepinephrine 0.05 μg kg^{-1} min^{-1} were commenced via a central vein to maintain arterial pressure at 95/50 mm Hg. After 1 h of i.v. 1% propofol sedation, mandatory pressure control ventilation with 100% oxygen, and no spontaneous respiratory efforts, arterial blood gas analysis showed pH 7.22, $P\mathrm{CO}_2$ 6.9 kPa, $P\mathrm{O}_2$ 64 kPa, and base excess –6.8 mmol litre^{-1}.

At this stage, detailed discussions regarding patient prognosis took place between all the relevant physicians and the patients' family. In view of the patient's age, premorbid state and presenting pathology, and the systemic insult of two episodes of hypoxia, the decision was taken not to escalate treatment further. Over the following 10 h, lung ventilation through the Combitube was continued, but the patient became progressively hypotensive and died.

Discussion

If the airway needs to be secured and tracheal intubation has failed, then the use of adjuncts may be life saving. The Combitube and LMA are included in the European Resuscitation Council guidelines for the management of the emergency airway.[1] Previous studies have confirmed the effectiveness of the Combitube in hospital-based cardiopulmonary resuscitation,[3 4] in the management of the trauma patient,[5] and in ventilation of the lungs both during routine surgery,[6] and on the intensive care unit.[7] Many difficult airway situations have been managed using the Combitube airway,[8–12] and it compares favourably with the LMA when used by unskilled staff.[13–16]

Management of the airway of a patient with halo frame cervical spine immobilization in place is difficult. The halo frame immobilizes the head and neck, and prevents 'sniffing the morning air' positioning for intubation, where the cervical spine is flexed and the craniocervical junction extended. Undue force used during laryngoscopy and tracheal intubation may move the cervical vertebrae and jeopardize the spinal cord. For these reasons, preference over direct laryngoscopy is usually given to awake fibreoptic tracheal intubation, or use of the intubating LMA. In this case, as discussed below, only the contents of the ward emergency airway trolley as described were immediately available. The author became involved during the second airway episode, at which point the Combitube was available from his personal supply.

The Combitube is designed for insertion in the neutral position, with the occiput on the flat surface on which the patient is positioned. Supine patients with Halo frame immobilization approach this position. Successful use of the Combitube in the *elective* anaesthetic airway management of a patient with Halo frame cervical spine fixation has been described.[17] The natural curve and rigidity of the Combitube facilitates its passage around the angle between the axis of the oral cavity and larynx. It, therefore, proved ideal in this case.

The recommended position for insertion of the LMA is 'sniffing the morning air'.[18] This is clearly not possible with a halo frame in place.

The LMA was successful in the first instance of emergency airway control, but failed after further craniocervical flexion during the second episode.

This is the first case described using the Combitube in the emergency management of the airway of a patient with halo frame cervical spine immobilization in place. It is also the first case of emergency airway management described where other airway techniques, including the use of the LMA, have failed and the Combitube succeeded. Moreover, airway obstruction caused by placement of a halo frame has not been reported. Pathology associated with the initial trauma, such as retropharyngeal haematoma, can cause obstruction, although in this case, no such abnormality was seen at initial laryngoscopy, and the post-mortem reported the upper airways as normal.

The cause of both acute deteriorations was airway obstruction following craniocervical junction flexion, the flexion being greater in the second instance (Fig. 3). However, this only became apparent after extubation on the ICU. The differential diagnosis initially included acute pulmonary oedema (although this was not evident clinically), cervical cord damage (although the patient moved all limbs throughout and no external cord abnormalities were seen at post-mortem examination), and tracheal mucus plugging (which was also not seen at post-mortem).

In hindsight, better equipment to manage the second episode should have been available on the operating theatre difficult airway trolley, which contained the intubating LMA and intubating fibrescope. Additionally, at any stage craniocervical deflexion may have alleviated the airway obstruction, but at the risk of compromising the cervical spinal cord.

When resuscitating the unconscious patient, where the 'sniffing the morning air' position is not achievable because the cervical spine is, or must be, immobilized in the neutral position, then the Combitube may be preferential to the LMA as an adjunct device, or for use by those not skilled in tracheal intubation. In this regard, inclusion of the Combitube in the emergency airway trolley would be beneficial, although this does assume the operator has prior experience of all of these airway techniques.

In conclusion, this case demonstrates the utility of the Combitube in the management of the emergency airway in a hitherto unreported setting. It has been demonstrated to be effective where other airway techniques have failed, and its inclusion in the European Resuscitation Council guidelines has been reiterated.

References

1 A Statement by the Airway and Ventilation Management Working Group of the European Resuscitation Council. Guidelines for the advanced management of the airway and ventilation during resuscitation. *Resuscitation* 1996; **31**: 201–30

2 Lipp M, Thierbach A, Daublander M, Dick W. Clinical evaluation of the 'Combitube'. Abstract to the 18th annual meeting of the European Academy of Anaesthesiology, Copenhagen, Denmark, August 29th to September 1st, 1996

3 Frass M, Frenzer R, Rauscha F, Weber H, Pacher R, Leithner C. Evaluation of esophageal combitube in cardiopulmonary resuscitation. *Crit Care Med* 1987; **15**: 609–11

4 Frass M, Frenzer R, Rauscha F, Schuster E, Glogar D. Ventilation with the Esophageal Tracheal Combitube in cardiopulmonary resuscitation. Promptness and effectiveness. *Chest* 1988; **93**: 781–4

5 Blostein PA, Koestner AJ, Hoak S. Failed rapid sequence intubation in trauma patients esophageal tracheal combitube is a useful adjunct. *J Trauma* 1998; **44**: 534–7

6 Frass M, Frenzer R, Zhadral F, Hoflehner G, Porges P, Lackner F. The esophageaaal tracheal Combitube: preliminary results with a new airway for CPR. *Ann Emerg Med* 1987; **16**: 768–72
7 Frass M, Frenzer R, Mayer G, Popovic R, Leithner C. Mechanical ventilation with the esophageal tracheal combitube (ETC) in the intensive care unit. *Arch Emerg Med* 1987; **4**: 219–25
8 Eichinger S, Schreiber W, Heinz T, *et al.* Airway management in a case of neck impalement: use of the oesophageal tracheal Combitube airway. *Br J Anaesth* 1992; **68**: 534–5
9 Klauser R, Röggla G, Pidlich J, Leithner C, Frass M. Massive upper airway bleeding after thrombolytic therapy: successful airway management with the Combitube. *Ann Emerg Med* 1992; **21**: 431–3
10 Wagner A, Roeggla M, Roeggla G, *et al.* Emergency intubation with the Combitube in a case of severe facial burn. *Am J Emerg Med* 1995; **13**: 681–3
11 Staudinger T, Tesinsky P, Klappacher G, *et al.* Emergency intubation with the Combitube in two cases of difficult airway management. *Eur J Anaesthesiol* 1995; **12**: 189–93
12 Banyai M, Falger S, Roggla M, *et al.* Emergency intubation with the Combitube in a grossly obese patient with bull neck. *Resuscitation* 1993; **26**: 271–6
13 Yardy N, Hancox D, Strang T. A comparison of two airway aids for emergency use by unskilled personnel. The Combitube and laryngeal mask. *Anaesthesia* 1999; **54**: 181–3
14 Tanigawa K, Shigematsu A. Choice of airway devices for 12 020 cases of nontraumatic cardiac arrest in Japan. *Prehosp Emerg Care* 1998; **2**: 96–100
15 Rumball CJ, MacDonald D. The PTL, Combitube, laryngeal mask, and oral airway: a randomized prehospital comparative study of ventilatory device effectiveness and cost-effectiveness in 470 cases of cardiorespiratory arrest. *Prehosp Emerg Care* 1997; **1**: 1–10
16 Doerges V, Sauer C, Ocker H, Wenzel V, Schmucker P. Airway management during cardiopulmonary resuscitation – a comparative study of bag-valve-mask, laryngeal mask airway and combitube in a bench model. *Resuscitation* 1999; **41**: 63–9
17 Deroy R, Ghoris M. The Combitube elective anesthetic airway management in a patient with cervical spine fracture. *Anesth Analg* 1998; **87**: 1441–2
18 Baskett PJF, Brain AIJ. *The Use of the LMA in Cardiopulmonary Resuscitation Handbook*, 1st edn. Intavent Ltd, September 1994; 6

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Intramuscular ketamine in a parturient in whom pre-operative intravenous access was not possible

W. C. Lum Hee* and V. F. Metias

Department of Anaesthesia, Barnsley District General Hospital NHS Trust, Gawber Road, Barnsley S75 2EP, UK

**Corresponding author. Present address: Department of Anaesthesia, C Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2SB, UK*

We describe the management of a 23-yr-old woman with extreme needle and mask phobia, presenting for an emergency Caesarean section for fetal distress. She also suffered from spina bifida cystica with no sensation from mid thigh. Regional anaesthesia, rapid sequence induction, and gaseous induction were not possible. She was managed successfully with i.m. ketamine followed by a more conventional anaesthetic technique.

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Patients with an aversion to either needles or masks are not uncommon, but those with a marked phobia to both are more rare, and can present an anaesthetic dilemma. However, in general, they can be persuaded to undergo either an i.v. induction, following the use of a topical local anaesthetic for cannulation, or a gaseous induction, with the promise of a pleasant smelling agent and a clear mask. In this case, we were presented with a patient who was

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adamant in her refusal to have both injections and a mask. This was further complicated by the urgent nature of the surgery—a Caesarean section for fetal distress.

The anaesthetic management of parturients with spina bifida cystica has been reported but there are no cases in the literature describing the management of such a patient in whom regional techniques, i.v. and gaseous induction were not possible.

Case report

A 23-yr-old female presented in the early hours of the morning, for an emergency Caesarean section for fetal distress at 29 weeks gestation. She suffered from spina bifida cystica and was wheelchair bound. She had a functioning ventricular peritoneal shunt *in situ* for hydrocephalus and was incontinent of both urine and faeces. She was taking prophylactic amoxycillin for recurrent urinary tract infections but was on no other medication. Her obstetric history consisted of a previous neonatal death at 22 weeks and a miscarriage at 8 weeks. She had numerous anaesthetics in the past, but none at this hospital.

This lady had been admitted electively the previous day for steroid therapy and was now having irregular contractions but was not in established labour. A CTG trace showed prolonged late decelerations. It was decided that a Caesarean section was needed and the patient, although initially reluctant, agreed and gave written consent. Until this time, she had not been referred to an anaesthetist.

The patient signed her consent form on condition that she would have a general anaesthetic and would not have any injections in her arms or have a mask. She was extremely needle phobic, and her notes were littered with previous refusals to have injections and blood tests. She was, however, willing to have a drip sited in her lower legs, as she 'would not feel it', as she was numb from mid thigh. This had been done for a previous anaesthetic. She refused to consider the use of a topical local anaesthetic, prior to siting a drip in her arms, saying that it 'doesn't work'.

She also refused to have oxygen administered pre-operatively, or to consider a gaseous induction and would not allow the use of cricoid pressure.[1] She would consent only to an injection into the insensate portion of her legs and was amenable to any necessary action being taken once she was unaware.

Examination revealed a female of short stature, with swollen oedematous legs, and no visible veins. We estimated her height as 130 cm and her weight as 40 kg (BMI=23). She was pigeon chested with a short neck but normal head, neck and jaw movement and a Mallampati[2] score of 2. She was also confirmed to be anaesthetic to mid thigh bilaterally.

The risks of a general anaesthetic and our proposed plan of action were clearly explained to her and were accepted. She was given sodium citrate as antacid prophylaxis and transferred to the obstetric theatre. She was placed in a supine position with a left lateral tilt. It was not possible to obtain venous access in her legs, so an i.m. injection of ketamine 400 mg (10 mg kg^{-1}) was administered. After a 10-min interval, the patient was sufficiently compliant for oxygen to be administered, cricoid pressure to be applied and an i.v. cannula sited (16 g in the right forearm). A conventional anaesthetic consisting of i.v. thiopentone 200 mg (5 mg kg^{-1}) and suxamethonium 100 mg was then administered. Intubation was performed without any difficulty and anaesthesia maintained with 30% oxygen, 70% nitrous oxide, and 1% isoflurane. Atracurium was given to maintain muscle relaxation. Monitoring included pulse oximetry, non-invasive arterial pressure, ECG, capnography, and ventilator alarms.

A live female infant was delivered 10 min later. She needed to be intubated and the 1 and 5 min APGAR scores were 5 and 9, respectively. She was taken to the Special Care Baby Unit but was transferred to the regional specialist neonatal unit 36 h later.

The remainder of the surgery and anaesthetic was uneventful. Post-operatively, the patient was kept on the obstetric HDU until the morning. When reviewed at that time, she was alert, pain free, and satisfied with her anaesthetic management. She had not required any analgesia. She was subsequently transferred with her baby to the regional centre.

Discussion

Spina bifida cystica occurs in 1–3 per 1000 births and is because of the failed closure of the neural arch with herniation of the meninges and or neural elements through the vertebral defect. It is associated with pre-term labour. Successful epidural anaesthesia has been described,[3] but may be unreliable below the level of the defect. However, in general, subarachnoid block[4] is effective. Unfortunately, in this case, the patient's severe needle phobia prohibited the use of either technique.

The risks of general anaesthesia in pregnant patients are considerable. The major risks are hypoxaemia[5] and aspiration.[5] It is for these reasons that pre-oxygenation and the use of cricoid pressure[1 5 6] are now routine in the administration of a general anaesthetic for all obstetric cases. However, our patient refused to allow the use of either and as the risks had been clearly explained, and were accepted by her, we proceeded.

We were faced with a patient who wished to have a general anaesthetic, but in whom we were unable to obtain pre-operative venous access. Furthermore, the usual alternative of a gaseous induction was also prohibited. This left us with three options: the use of a large dose of sedative premedicant orally, the administration of an agent rectally, or the use of an i.m. agent. We felt that an oral pre-med would have had an adverse effect on the already distressed foetus, and would have been more time consuming. For similar reasons, we did not consider a rectal agent particularly in view of her incontinence.

We opted for ketamine i.m., as its use in Caesarean sections is well described.[7–9] It has good haemodynamic properties[8] and does not cause neonatal depression.[7–9] Its use by the i.m. route is less common, and is reserved mainly for the management of difficult children.[10] It is associated with nightmares in the recovery period, but in this case none were reported. We did not give any opioids or benzodiazepines, which are often used to attenuate these, but did ensure a quiet environment for recovery. Further, ketamine has analgesic properties,[11] which undoubtedly contributed to the pain free state of the patient postoperatively. However, the complete lack of analgesic requirements may not be attributable solely to the ketamine, and may be because of an altered sensation on the part of the patient.

We used a 'normal' induction dose of thiopentone (5 mg kg $^{-1}$) before intubation. We acknowledge that this was probably a larger dose than was needed in a lady who had already been given ketamine but wished to ensure unconsciousness in a patient in whom ketamine had yet to reach full effect.

This case illustrates the need for close co-operation between the obstetric and anaesthetic departments. This was a patient in whom obstetric intervention was highly likely, and who was clearly going to be difficult to manage. In addition, she was an inpatient for steroid therapy, because of the risk of early labour. However, she was not brought to our attention until late at night when the decision to perform an emergency Caesarean section had been made. Early referral to an anaesthetist may not have altered our subsequent management but would have given us time to plan. Furthermore, interview of the patient under less fraught circumstances, and frank discussion of all the options and risks may have resulted in a more co-operative and less anxious patient and would have expedited the delivery of the distressed baby.

References

1 Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; **2**: 404–6

2 Mallampati SR, Gatt SP, Gugino LP, *et al.* A clinical sign to predict difficult intubation: a prospective study. *Can Anaesth Soc J* 1985; **32**: 429–34

3 Vaagenes P, Fjaerestad I. Epidural block during labour in a patient with spina bifida cystica. *Anaesthesia* 1981; **36**: 299–301

4 Broome I J. Spinal anaesthesia for Caesarean section in a patient with spina bifida cystica. *Anaesth Intensive Care* 1989; **17**: 377–9

5 Morgan M. Obstetric anaesthesia and analgesia. In: Nimmo WS, Rowbotham DJ, Smith G, eds. *Anaesthesia*, 2nd edn. Oxford: Blackwell Scientific Publications, 1994; 1000–25

6 Roberts RB, Shirley MA. Reducing the risk of acid aspiration during Caesarean section. *Anesth Analg* 1974; **53**: 859–68

7 Peltz B, Sinclair DM. Induction agents for Caesarean section: a comparison of thiopentone and ketamine. *Anaesthesia* 1973; **28**: 37–42

8 Schultetus RR, Paulus DA, Spohr GL. Haemodynamic effects of ketamine and thiopentone during anaesthetic induction for Caesarean section. *Can Anaesth Soc J* 1985; **32**: 592–6

9 Baraka A, Louis F, Dalleh R. Maternal awareness and neonatal outcome after ketamine induction of anaesthesia for Caesarean section. *Can J Anaesth* 1990; **37**: 641–4

10 Scott K, Eltringham RJ. Anesthetic dilemmas: the uncontrollable child. *Br J Hosp Med* 1992; **47**: 357

11 Kee WD, Khaw KS, Ma ML, Mainland PA, Gin T. Postoperative analgesic requirement after Cesarean section: a comparison of anesthetic induction with ketamine or thiopental. *Anesth Analg* 1997; **85**: 1294–8

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Cranial subdural haematoma after spinal anaesthesia

R. Acharya[1]*, S. S. Chhabra[1], M. Ratra[2] and A. D. Sehgal[1]

[1]Department of Neurosurgery, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India. [2]Department of Anaesthesiology, Mata Chanan Devi Hospital, New Delhi, India

**Corresponding author*

Intracranial subdural haematoma is an exceptionally rare complication of spinal anaesthesia. A 20-yr-old male underwent appendicectomy under partial spinal and subsequent general anaesthesia. A week later, he presented with severe headache and vomiting not responding to bed rest and analgesia. Magnetic resonance imaging showed a small acute subdural haematoma in the right temporo-occipital region. The patient improved without surgical decompression.

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The pathogenesis of headache and subdural haematoma formation after dural puncture is discussed and the literature briefly reviewed. Severe and prolonged post-dural puncture headache should be regarded as a warning sign of an intracranial complication.

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The most common complication of spinal anaesthesia is headache. Post-dural puncture headache (PDPH) is classically postural and responds within 48 h to increased fluid intake and bed rest. Prolonged PDPH may be caused by subdural haematoma[1–4] or intracerebral haemorrhage.[5] Few anecdotal cases of this neurological complication are described in the literature. We report a case of cranial subdural haematoma in a patient who underwent spinal anaesthesia for appendicectomy.

Case report

A 20-yr-old male was admitted with abdominal pain and vomiting. Acute appendicitis was diagnosed and appendicectomy was performed under spinal anaesthesia. A 23G Quincke point spinal needle was introduced through the L4–5 interspace. After dural puncture at the first attempt, 1.8 ml of 0.5% heavy bupivacaine was injected. This was only partially effective, so general anaesthesia was induced with thiopentone 200 mg, succinylcholine 80 mg and atropine 0.6 mg. Anaesthesia was maintained with 0.5% halothane, pentazocine 30 mg and midazolam 1 mg. Muscle relaxation was maintained by a further dose of succinylcholine 80 mg given 20 min later. The patient remained haemodynamically stable. The excised appendix was grossly inflamed; histopathology confirmed the diagnosis of acute appendicitis.

The patient recovered fully and was discharged on the third day after the operation. He had no headache at the time of discharge. However, a week later, he developed a severe diffuse headache which did not subside with analgesia and bed rest. When he started to vomit, an intracranial lesion was suspected and a neurosurgical consultation was sought. There was no history of fever, trauma or bleeding diathesis. On examination, the patient was conscious and oriented: Glasgow coma score was 15, fundi were normal and there was no focal neurological deficit. He had no neck rigidity or Kernig's sign. Haemoglobin, total and differential leucocyte counts, platelet count, bleeding time, clotting time, prothrombin time and activated partial thromboplastin time (APTT) were normal. Biochemical values, including liver and renal function tests, were also normal.

Magnetic resonance imaging of the head showed a small acute subdural haematoma in the right temporo-occipital region with no mass effect. The patient was managed conservatively with bed rest, analgesia and intravenous fluids. He recovered completely and was discharged after a week.

Discussion

Headache is the most frequent complication after lumbar puncture, occurring in ≤40% of cases.[6] Such headaches are thought to be caused by excessive (≤250 ml day^{-1})[7] leakage of cerebrospinal fluid (CSF) through the dural puncture, causing caudal displacement of intracranial structures.[8] This displacement then stretches the intracranial pain-sensitive dura, sinuses and blood vessels, causing pain. Typical PDPH may occur soon after spinal anaesthesia and usually subsides in a few days with bed rest and analgesia. Recently, Suess and colleagues found that headache lasting >5 days was the chief complaint in 17 reported cases of intracranial haemorrhage after myelography.[9] Macon and colleagues reported that headache of subdural haematoma was more severe than PDPH and persistent, even in the recumbent position.[10] PDPH was the most frequently encountered complication with traditional Quincke point spinal needles of large size. Its incidence has been minimized with the use of 29G needles[11] and pencil-point needles.[12] Epidural blood patching has been described for stopping CSF leakage, thereby relieving the headache.[13]

Subdural haematomas have occurred after lumbar puncture in association with cerebral aneurysm, brain tumour, recent cerebrovascular accident and meningovascular syphilis. It is postulated that the haemorrhage is caused by a sudden decrease in intracranial pressure consequent to the loss of CSF at the lumbar puncture site. Sudden caudal shift of the brain may cause traction on the arachnoid mater and/or venous structures and may lead to bleeding from ruptured vessels. Thorsen has described multiple petechial haemorrhages on the surface of the brain after spinal anaesthesia.[14] Pavlin and colleagues reported two cases of large subdural haematoma, which required surgical evacuation.[1] Mantia reported a case of intracerebral haemorrhage after lumbar puncture with a 26G spinal needle; his patient improved with conservative treatment.[5]

The true incidence of subdural haematoma after dural puncture is not known. Most patients with headache are probably treated without investigation. Subdural haematomas are known to resolve spontaneously[15] but they may be catastrophic as evident from the deaths recorded as a complication of lumbar puncture.[9 16] In the case described here, the patient developed a subdural haematoma despite the use of a narrow gauge (23G) spinal needle. Altered CSF dynamics probably caused the rupture of a cerebral vein, resulting in the development of a subdural haematoma. Fortunately, the haematoma was only small and did not require surgical decompression.

Severe and prolonged PDPH should be regarded as a warning sign of an intracranial haematoma. In these patients, early neurosurgical consultation is recommended.

References

1 Pavlin DJ, McDonald JS, Child B, *et al.* Acute subdural hematoma—an unusual sequela to lumbar puncture. *Anesthesiology* 1979; **51**: 338–40

2 Vaughan DJA, Stirrup CA, Robinson PN. Cranial subdural haematoma associated with dural puncture in labour. *Br J Anaesth* 2000; **84**: 518–20

3 Rudehill A, Gordon E, Rahn T. Subdural haematoma: a rare but life-threatening complication after spinal anaesthesia. *Acta Anaesthesiol Scand* 1983; **27**: 376–7

4 Velarde CA, Zuniga RE, Leon RF, *et al.* Cranial nerve palsy and intracranial subdural hematoma following implantation of intrathecal drug delivery device. *Regional Anaesth Pain Med* 2000; **25**: 76–8

5 Mantia AM. Clinical report of the occurrence of an intracerebral hemorrhage following post-lumbar puncture headache. *Anesthesiology* 1981; **55**: 684–5

6 Alemohammad S, Bouzarth WF. Intracranial subdural hematoma following lumbar myelography. *J Neurosurg* 1980; **52**: 256–8

7 Frankson C, Gordth T. Headache after spinal anaesthesia and a technique for lessening its frequency. *Acta Chir Scand* 1964; **94**: 413

8 Gass H, Goldstein AS, Ruskin R, *et al.* Chronic post-myelogram headache. Isotopic demonstration of dural leak and surgical cure. *Arch Neurol* 1971; **25**: 168–70

9 Suess O, Stendel R, Baur S, *et al.* Intracranial haemorrhage following lumbar myelography: case report and review of the literature. *Neuroradiology* 2000; **42**: 211–14

10 Macon ME, Armstrong L, Brown EM. Subdural hematoma following spinal anesthesia. *Anesthesiology* 1990; **72**: 380–81

11 Flaaten H, Rodt SA, Vamnes J, *et al.* Post-dural puncture headaches: a comparison between 26 and 29G needles in young patients. *Anaesthesia* 1989; **44**: 147–9

12 Hart JR, Whitacre RJ. Pencil point needle in prevention of post spinal headache. *J Am Med Assoc* 1951; **147**: 657–8

13 Abouleish E, Vega S, Blendinger I, *et al.* Long-term follow-up of epidural blood patch. *Anesth Analg* 1975; **54**: 459–63

14 Thorsen G. Neurological complications after spinal anaesthesia and results from 2,493 follow-up cases. *Acta Chir Scand* 1947; **95** (Suppl 121): 1–272

15 Blake DW, Donnan G, Jensen D. Intracranial subdural haematoma after spinal anaesthesia. *Anaesth Intens Care* 1987; **15**: 341–2

16 Newrick P, Read D. Subdural haematoma as a complication of spinal anaesthetics. *Br Med J* 1982; **285**: 341–2

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Correspondence

Unilateral bronchospasm

A recent issue of the *British Journal of Anaesthesia* contained a case report[1] of severe unilateral bronchospasm secondary to the use of a Laryngojet lidocaine spray. This report had been discussed within our anaesthetic department 1 week before an incident occurred during a routine case, which we believe to be another example of the same problem. Knowledge gained directly from the report assisted in the prompt diagnosis and treatment of our patient.

A 67-year-old, 55 kg woman was scheduled for craniotomy and debulking of a temporoparietal tumour. Her past medical history included hypertension and heavy smoking. Anaesthesia was induced with fentanyl, propofol, and atracurium. Under direct vision, a Laryngojet injector was used to spray the vocal cords with 4% lidocaine. A size 6.5 reinforced tracheal tube was inserted without difficulty. The chest immediately felt 'tight' and was difficult to ventilate, but this resolved after several manual breaths. Anaesthesia was maintained with oxygen/air/sevoflurane and a remifentanil infusion.

In the operating theatre, it was noticed that the patient's left chest was not moving and was silent on auscultation. Monitoring revealed an Sp_{O_2} of 99% and a $P\acute{E}'_{CO_2}$ of 4.4 kPa with a normal respiratory trace. Because of the recent report, we suspected unilateral bronchospasm, but other causes were excluded first. The dressing around the tracheal tube was removed and the position of the tube found to be correct on laryngoscopy. A suction catheter passed easily through the tube and only a small amount of greenish sputum was removed. The left chest remained silent and immobile. Blood gases at this time revealed pH 7.35, P_{CO_2} 7.0 kPa, and P_{O_2} 13.2 kPa ($F_{I_{O_2}}$ of 0.4).

Salbutamol 250 μg (approximately 5 μg kg^{-1}) was given as a slow intravenous bolus. The left chest immediately started to rise on inflation, the E'_{CO_2} rose to 5.6 kPa, and the Sp_{O_2} fell to 94–95%. The left chest remained quiet on auscultation, except for some expiratory wheeze. An infusion of salbutamol (250 μg over 1 h) was commenced and surgery was allowed to proceed. Breath sounds and blood gases returned to normal. The tracheal tube was removed at the end of the operation and the patient admitted to the intensive care unit.

In contrast to the earlier case report,[1] our patient's oxygen saturation was well maintained until the bronchospasm improved. The most likely explanation is that there was almost no flow of blood through the unventilated left lung due to extensive hypoxic pulmonary vasoconstriction (HPV). When some ventilation returned, the HPV partially reversed, leading to ventilation/perfusion mismatch. The pulmonary vasodilator effect of salbutamol may have also contributed to this effect.

N. Smith
P. Nandi
London

1 Farmery AD. Severe unilateral bronchospasm mimicking inadvertent endobronchial intubation: a complication of the use of a topical lidocaine Laryngojet injector. *Br J Anaesth* 2000; **85**: 917–9

Editor—Thank you for the opportunity to comment on the report of Drs Smith and Nandi. It is gratifying that the report in this journal of my similar experience was of some help in their quick diagnosis and management of the incident. Dr Smith reports another interesting observation: namely that deterioration of their patient's gas exchange was apparent not *during* the ventilatory abnormality, but *after* it had been corrected. They propose a plausible mechanism for this, and I would like to add a few other comments.

A simple (but probably less plausible) mechanism for the asynchrony between the onset of the ventilatory abnormality and the onset of arterial desaturation is that in apnoea, the latter always lags behind the former. If small airway bronchospasm occurred suddenly, it is possible that a significant reservior of alveolar oxygen was trapped distal to the conducting airways, and a mathematical model[1] predicts that this may buy several minutes of normoxaemia before arterial desaturation occurs. Eventually the alveolar reserve is consumed, and absorption atelectasis develops. If this desaturation happens to coincide with the reverasl of bronchospasm, there would appear to be a paradoxical temporal relationship between the resumption of effective ventilation and the onset of arterial desaturation.

It is interesting to consider the role of V/Q mismatch, shunt and hypoxic pulmonary vasoconstriction (HPV) in this process. The clinical details described by Dr Smith suggest that ventilation to the left lung was markedly reduced, or almost absent. However, during this period the patient was remarkably well oxygenated (Sp_{O_2} of 99%, Pa_{O_2} 13.2 kPa). One mechanism for this, favoured by Dr Smith, is that blood flow to the unventilated lung was almost totally abolished due to HPV and so V/Q matching was very well preserved.

By combining the well known 'shunt' and Fick mass balance equations, and estimating the cardiac output to be somewhat reduced, the recovered true shunt fraction can indeed be shown to be small (approximately 5–10%). However, this does not necessarily mean that the blood flow to the left lung was very small. In fact, there is evidence to suggest that the blood flow to the left lung was appreciable.

In this patient, there is a marked difference between end-tidal (4.4 kPa) and arterial (7.0 kPa) P_{CO_2}. There are two main possibilities for this observation. One is that the end-tidal gas is not 'true' alveolar gas (and hence arterial equivalent) but that it is *diluted* by significant parallel alveolar deadspace gas throughout expiration. It seems unlikely that this is this case because: (i) the predominant abnormality is a discrete low V/Q region in the left lung; and (ii) although the entire right lung is a region of relatively high mean V/Q, it is presumably fairly homogeneous (as evidenced by the 'normal' capnogram) and so end-tidal P_{CO_2} was probably a true reflection of alveolar and end-capillary P_{CO_2} from this well-ventilated region. The second, and most likely possibility is that there is a significant blood flow to the low V/Q region. This is distinct from 'true shunt' which we have estimated to be small. Blood leaving this compartment will be just about adequately oxygenated with an $F_{I_{O_2}}$ of 0.4, but its P_{CO_2} will be essentially identical to mixed-venous blood which itself is likely to be elevated in view of the low cardiac output. When this blood mixes with that leaving the well-ventilated alveoli of the right lung (with an end-capillary P_{CO_2} close or equal to end-tidal P_{CO_2}), the resultant mixed arterial blood P_{CO_2} is elevated, creating the observed 'a–A' P_{CO_2} diffence. Using estimates of CO_2 content[2] in the mass balance equations mentioned above, the flow to the low V/Q compartment may have been as high as 30–40% of total cardiac output, indicating that the effect HPV was only modest.

Is it possible that with the resumption of alveolar ventilation to the left lung, HPV was reversed and worsened the V/Q mismatch? Although increasing PA_{O_2} (with the resumption of ventilation)

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would result in an increased blood flow, this blood would now be equilibrating with the increased PA_{O_2} and so cannot be regarded as 'shunt' (unless of course there is some hysteresis in the relationship between PA_{O_2} and HPV).

Dr Smith's observations appear to fit exactly with an experimental model published very recently by Russell and James.[3] These researchers hypothesized that if a shunt (or region of very low V/Q) existed, then an increase in cardiac output should theoretically improve arterial oxyhaemoglobin saturation because an increased cardiac output would reduce venous oxygen extraction and increase mixed venous oxyhaemoglobin saturation. However, they found that increasing the cardiac output with isoprenaline during one-lung ventilation in pigs actually resulted in a *fall* in arterial saturation. They concluded that although increasing the cardiac output in this way increased mixed venous saturation, this was more than offset by the increased shunting which isoprenaline (amongst other agents) appeared to induce. In Dr Smith's patient, who was experiencing something very similar to one-lung ventilation, injection of salbutamol 250 mcg would have effected a similar increase in cardiac output. Like Russell and James's pigs, despite this producing an increase in mixed venous saturation, the increased 'shunt', or flow to very low V/Q regions, would have produced arterial desaturation.

Marshall[4] proposed that the HPV response of pulmonary arteries was a function of both alveolar and mixed-venous oxygen tension as follows:

$$\text{'HPV sensitivity'} = PA_{O_2}{}^{0.62}.\ Pv_{O_2}{}^{0.38}$$

So an intropic bronchodilator will affect HPV sensitivity through both increasing Pv_{O_2} (as cardiac output is increased) and increasing PA_{O_2} (as effective ventilation is increased). If the inotropic response is more rapid than the exponential wash-in process of the increasing PA_{O_2}, it is possible that blood flow to the low V/Q region (as stimulated by the increase in Pv_{O_2}) may increase at a time when the PA_{O_2} is still low (but rising slowly). In this way V/Q mismatch will indeed be worsened. In addition, as Dr Smith points out, salbutamol ifself may have direct effects on pulmonary blood flow distribution.

It is likely that all of the above mechanisms (and doubtless many others) may contribute in various degrees to this interesting observation.

A.D. Farmery
Oxford

1 Farmery AD, Roe PG. A model to describe the rate of oxyhaemoglobin desaturation during apnoea. *Br J Anaesth* 1996; **76**: 284–91

2 McHardy G. The relationship between differences in pressure and content of carbon dioxide in arterial and venous blood. *Clin. Sci.* 1967; **32**: 299–309

3 Russell WJ, James MF. The effects on increasing cardiac output with adrenaline or isoprenaline on arterial haemoglobin oxygen saturation and shunt during one-lung ventilation. *Anaesth Intensive Care* 2000; **28**: 636–41

4 Marshall B, Marshall C. Active regulation of the pulmonary circulation: a model for hypoxic pulmonary vasoconstriction. In: Will J, Dawson CA, Weir EK, Buckner CK, eds. *The Pulmonary Circulation in Health and Disease*, 1st Edn. Orlando, Florida: Academic Press Inc., 1987: 256

Peri-operative β-blockade

Editor—I was pleased to read the well-balanced arguments surrounding the peri-operative use of β-blockers.[1] However, there are a number of issues that I still feel need to be addressed. There is undoubtedly support for the wider use of β-blockers in patients with an intermediate or low cardiac risk,[2–4] in addition to the isolated high risk subgroup studied by Poldermans.[5] Indeed, Priebe in a recent review stated that 'the maintenance of, or initiation of, β-adrenoreceptor blocker therapy in the peri-operative period with the aim of maintaining heart rate at < 80 beats min^{-1} must now be considered standard practice in the peri-operative management of the aged patient at risk for, or having, ischaemic heart disease'.[4]

I am not aware that this is standard practice in the UK and, as Howell and colleagues suggest, the current evidence supporting the 'acute' use of β-blockers in the peri-operative period is far from overwhelming. It is dangerous to assume that one can extrapolate the current findings and apply them to an entirely different patient group.

I would concur with the points raised about the timing, the length of treatment, and the value of these drugs when additional sympatholytic therapies are used, such as epidurals. In addition, we should consider how these drugs could affect the management of non-cardiac complications.

The recognition and treatment of peri-operative haemorrhage or sepsis may be hindered if the patient is unable to mount an adequate sympathetic response. This is particularly important as a significant proportion of these patients are elderly and thus have a relatively non-compliant cardiovascular system. Poldermans reported no non-cardiac deaths in his study[5] and although Mangano[6] reported the number of deaths from non-cardiac causes, there were no further details. Significant morbidity and mortality from surgical complications may not have been apparent given the relatively small numbers of patients in both studies.

Futhermore, should we be thinking of using these drugs only in elective surgery? The problems of their use in urgent or emergency surgery have not been discussed, but would the cardioprotective effect be outweighed by the risk of exaggerated cardiovascular instability in the face of haemorrhage or sepsis?

These are important points to address as the wider use of β-blockers may necessitate increased vigilance particularly in the post-operative period. Whether this is reflected in demands upon nursing and critical care services remains to be seen, but larger randomized controlled trials are needed to focus on these issues.

R.A. Ellis
Manchester
UK

1 Howell SJ, Sear JW, Foex P. Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm. *Br J Anaesth* 2000; **86**: 161–4

2 Lee TH. Reducing cardiac risk in noncardiac surgery. *New Engl J Med* 1999; **24**: 1838–40

3 Warltier DC. β adrenergic-blocking drugs. *Anesthesiology* 1998; **88**: 2–4

4 Priebe H-J. The aged cardiovascular risk patient. *Br J Anaesth* 2000; **85**: 763–78

5 Poldermans D, Boersma E, Bax JJ *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *New Engl J Med* 1999; **341**: 1789–94

6 Mangano DT, Layug EL, Wallace A, Tateo I, for the Multicenter Study of Perioperative Ischaemia Research Group. Effects of atenolol on mortality and cardiovascular morbidity after non-cardiac surgery. *New Engl J Med* 1996; **335**: 1713–20

Editor— We thank Dr Ellis for his interest and comments on our recent editorial on the peri-operative use of β-adrenoceptor blocking drugs. While we would accept the argument in favour of the use of these drugs in high-risk patients (as typified by the patients in the study of Poldermans and colleagues),[1] we are still awaiting good quality evidence of their efficacy and lack of adverse side-effects in the low and intermediate risk patient groups.

As far as we know, there are no data examining the effects of β-adrenoceptor blockade in patients undergoing urgent or emergency surgery, and hence we cannot comment on whether the cardioprotective effects of the drugs will outweigh the risk of exaggerated cardiovascular instability in the face of haemorrhage, hypovolaemia or sepsis.

Among other considerations is the question of when the drugs (if used) should be started; our previous data[2] suggest that a single oral or i.v. dose prior to surgery followed by i.v. or oral post-operative dosing may offer cardiac advantages, but does this make 24–48 h of post-operative intensive monitoring mandatory? Currently available data highlight the complexity of the issues raised by the suggestion that β-blockade could be used in the peri-operative period in haemorrhage or sepsis. β-adrenoceptor blockers have been shown to interfere with platelet aggregation in patients with stable angina[3]. Would this effect be observed in emergency surgical patients? There is evidence from animal studies that β-adrenoceptor blockade may interfere with immune function.[4] While it was the feeling of Katafuchi[4] that β-adrenoceptor blockade should be avoided in patients dependent on sympathetic drive for cardovascular stability, it is now clear that β-adrenergic blockade may offer benefits to patients in heart failure.[5] In the light of these complexities, we feel that the issue of the use of β-adrenoceptor blockers in emergency surgery or septic patients has to be addressed by proper randomized controlled trials.

Thus, until these trials provide us with firm clinical outcome data, we would afford caution to the use of β-adrenoceptor blockade in such urgent and emergency patient populations.

John Sear
Nuffield Department of Anaesthetics
University of Oxford
UK

Simon Howell
Department of Anaesthesia
University of Bristol
UK

1 Poldermans D, Boersma E, Bax JJ *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *New Engl J Med* 1999; **341**: 1789–94
2 Stone JG, Foex P, Sear JW *et al.* Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. *Anesthesiology* 1988; **68**: 495–500
3 Winther K, Willich SN. β1 blockade and acute coronary ischaemia. Possible role of platelets. *Circulation* 1991; **84**(Suppl 6): 68–71
4 Katafuchi T, Take S, Hori T. Roles of sympathetic nervous system in the suppression of cytotoxicity of splanchnic natural killer cells in the rat. *J Physiol* 1993; **465**: 343–57
5 Dargie HJ, Lechat P. The cardiac insufficiency bisoprolol study II (CIBIS II: a randomised trial). *Lancet* 1999; **353**: 9–13

Production of human albumin solution: a continually developing colloid

Editor—We would like to commend Matejtschuk and colleagues for their informative review article on human albumin solution.[1] A great deal of information was provided about the clinical applications of these solutions. On a practical note, however, no explanation was offered for the use of glass bottles in the presentation of the final product. We wondered if there were good reasons for the glass bottles. We were unable to find a reference for this method of storage and wondered why albumin solution is the only commonly used colloid in the operating theatre to be packaged in glass. The full containers are heavy, unwieldy to carry and hang up (requiring a specific plastic harness), and prone to accidental breakage. Glass bottles require to be vented with an expensive and specfic air inlet device, with the attendant risk of venous air embolism. In addition, if rapid transfusion of colloid is indicated, there is no acceptable method of increasing the flow rate from the bottle. These issues become yet more significant in the emergency situation where hypovolaemia is severe.

Must human albumin solutions be presented in glass bottles?

N. Coker
P. Amoroso
Homerton Hospital
London
UK

1 Matejtschuk P, Dash CH, Gascoigne EW. Production of human albumin solution: a continually developing colloid. *Br J Anaesth* 2000; **85**: 887–95

Editor—We thank Coker and Amoroso for their appreciative comments on our review of the manufacture and clinical use of albumin. They pose a challenging question: must albumin solutions be presented in glass bottles? While we can appreciate the benefits described in terms of ease of administation, avoidance of accidental breakage, and capacity for enhanced delivery rates with plastic containers, to the best of our knowledge, all of the commerical manufacturers of albumin worldwide still only supply albumin in glass bottles.

Several arguments point to the benefits of the glass container. First, use of plastics raises the risk of leaching of plasticisers used in the polymerization process, and this risk might be accentuated by the known physiological binding properties of albumin. Any such leaching might also be exacerbated by the Pharmacopoieal requirement for the pasteurization of albumin solutions to be performed in the final container (for at least 10 h at 60°C). Soft plastic containers can also allow increased oxygen permeability, again aggravating protein oxidation.

Before a change to plastic containers could be licensed by the regulatory authorities, substantial stability studies would be needed, to demonstrate that albumin remained unaffected throughout its long shelf-life at ambient temperature. Finally, there is the Pharmacopoieal requirement for a demanding visual inspection of the albumin product in its final presentation prior to batch release, but subsequent to an incubation period at an elevated storage temperature, in order to detect any microbial growth. The optical properties of potential plastic replacement containers do not compare with those offered by glass.

In conclusion, we can understand the desire to see albumin supplied in plastic containers. Although such containers are widely used for non-proteinacious substances, they are rarely used for therapeutic proteins. The considerable technical obstacles related to the unique physiological and chemicophysical properties of albumin mean that we must continue to use glass, at least for the foreseeable future.

P. Matejtschuk
C.H. Dash
E.W. Gascoigne
Bio Products Laboratory
Elstree
UK

Loss of consciousness following spinal anaesthesia for Caesarean section

Editor—I should like to report a similar case of loss of consciousness after a spinal block for Caesarean section to that of Chan and colleagues.[1]

A 27-year-old primiparous patient from Zaire presented for an emergency Caesarean section for intra-uterine growth retardation and breech position. She spoke no English (an attending midwife translated). She had no past medical or psychiatric history or allergies and had had an uneventful spinal anaesthetic for an appendectomy in Zaire some years before. She was sickle cell negative

Routine antacid prophylaxis was given and she was positioned sitting on the operating table for a spinal anaesthetic. She was preloaded with Hartmann's 0.5 litre and after free flow of cerebrospinal fluid, hyperbaric 5% bupivacaine 2.2 ml with fentanyl 20 μg was given via a 25 gauge pencil point spinal needle. She was then positioned with left lateral tilt and oxygen 6 litre min^{-1} was given via a Hudson mask. Even with the midwife's help, it was very difficult to assess the height of the block but an absent reponse to painful stimulus was noted to at least T9 bilaterally before skin preparation. Standard monitoring was used (pre-incision: arterial pressure heart rate 85 beats 145/95 mm Hg, min^{-1}, SpO$_2$ 99%).

The patient appeared comfortable throughout the early stages of the operation, keeping her eyes shut through choice. Verbal contact was maintained every 30–60 s to reassure the patient and to check comfort and well-being.

Very soon after delivery of the placenta she was noted to be unresponsive with a Glasgow Coma Score of 3. During the third state of labour she had received oxytocin 10 iu and cefuroxime 1.5 g. There had been a lowering of arterial pressure from 140/80 mm Hg to 102/50 mm Hg but no hypoxia or bradycardia. Despite vigourous attempts to rouse her and with no detectable respiratory effort, it was decided to intubate the patient's trachea. She was ventilated with 100% oxygen by face mask with cricoid pressure, given succinylcholine 100 mg and the airway secured with a size 7 cuffed tracheal tube. Her pupils were mid-sized. An inadvertent drug error was immediately discounted.

The remainder of the operation was uneventful and spontaneous respiration resumed after 10 min. The arterial pressure returned to 145/80 mm Hg over the next 15 min. The tracheal tube was removed when the patient was awake and in the left lateral position. She had no residual deficit in the recovery room, but described feeling as if she had 'been a long way away' with no specific recollection of receiving bag and mask ventilation or of intubation.

A high spinal, although possible, would have been unlikely due to the volume of drug used, the time after the spinal that loss of consciousness occurred (25 min), and the absence of warning symptoms or signs. Other differentials including a subdural block, paradoxical embolism, or eclamptic fit (with absent or unnoticed epiliptiform movements) seemed unlikely as did a simple faint due to the lack of preceding hypotension or bradycardia. Although almost impossible to prove, an hysterical faint is a possible cause. But this must not detract from the importance of constant contact with patients undergoing regional techniques; vigilance must be observed at all times throughout the procedure.

Julian Stone
Anesthetic Department
Kingston Hospital
Surrey
UK

1 Chan YK, Gopinthan R, Rajendram R. Loss of consciousness following spinal anaesthesia for Caesarean section. *Br J Anaesth* 2000; **85**: 474–6

Complete recovery of consciousness in a patient with decorticate rigidity following cardiac arrest after thoracic epidural injection

Editor—We read with interest the report of complete recovery of consciousness in a patient with decorticate rigidity following cardiac arrest.[1] We are, however, astonished by use of the intracardiac route and not the peripheral or central venous route, for epinephrine injection in an adult patient during in-hospital cardiopulmonary resuscitation (CPR). Although no complications occurred with this procedure, we would like to advocate the intravenous or intratracheal route for epinephrine injection during CPR.

It is well known that intracardiac injection may be associated with serious complications such as cardiac tamponade,[2] coronary artery laceration, and pneumothorax. In addition, accidental lung injuries during intracardiac injection and positive pressure ventilation may increase the risk of systemic gas embolism, which may lead to catastrophic consequences.[3] The only possible advantage of intracardiac injection over the peripheral or central venous route is rapid arrival of the drug to the coronary circulation. This does not, however, seem to play an important role when basic CPR and proper airway management are established. The guidelines for cardiopulmonary resuscitation and emergency cardiac care[4] clearly indicate that intracardiac administration is to be used only during open cardaic massage or when other sites are unavailable.

Yoshihisa Fujita,
Michihisa Fuchimoto
Atsuo Sari
Kurashiki
Japan

1 Taga K, Tomita M, Watanabe I, et *al.* Complete recovery of consciousness in a patient with decorticate rigidity following cardiac arrest after thoracic epidural injection. *Br J Anaesth* 2000; **85**: 632–4
2 Martens PR. Intracardiac injection. *Resuscitation* 1992; **27**: 177
3 Ho AM, Ling E. Systemic air embolism after lung trauma. *Anesthesiology* 1999; **90**: 564–75
4 American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Part III. Adult advanced cardiac life support. *JAMA* 1992; **268**: 2199–241

Editor—We thank Dr Fujita and colleagues for their interest in our paper.[1] A resident performed the epidural block. We instruct the residents to secure an intravenous line and start the infusion of an electrolyte solution before proceeding with an epidural block in any elderly or poor risk patient in the outpatient pain clinic and also in all patients undergoing surgery in the operating room.[2]

This patient had been receiving single thoracic epidural injections (1% lidocaine 3 ml + 0.125% bupivacaine 3 ml) in our clinic for several months. There had been no previous complications such as a decrease in blood pressure or difficulty in breathing in this patient until the day the accident happened.

We were very busy on that day; many patients were waiting for treatment. The resident started an epidural block without an intravenous line. The resident said that he observed the patient for several minutes after the epidural block. In spite of achieving uncomplicated epidural block during this time, a nurse found the patient unconscious approximately 20 min after the block.

We agree that intracardiac administration of epinephrine should be used only during open cardiac massage.[3] However, we did not have an intravenous route to give the patient epinephrine. Moreover, we did not know for how long the patient had been apnoeic or had arrested. We therefore simultaneously gave cardiopulmonary resuscitation and an intracardiac injection of epinephrine to obtain rapid delivery of drug to the coronary circulation as Dr. Fujita and colleagues suggested.

We have strictly instructed the residents to secure an intravenous line before any epidural block procedures since the accident happened.

K. Taga[1]
M. Tomita[1]
I. Watanabe[2],
K. Sato[2]
K. Awamori[3]
H. Fujihara[1]
K. Shimoji[1]
[1]Department of Anaesthesiology
[1]Intensive Care Unit
[3]Department of Neurology
Niigata University School of Medicine
Japan

1 Taga K, Tomita M, Watanabe I, *et al.* Complete recovery of consciousness in a patient with decorticate rigidity following cardiac arrest after thoracic epidural block. *Br J Anaesth* 2000; **85**: 632–4

2 Shimoji K, Matsuki M, Shimizu H, Maruyama Y. The effects of epidural lidocaine on spinal cord and peripheral nervous activities in man. In: Wüst HJ, Stanton-Hicks M d'Arcy, eds. *New Aspects in Regional Anaesthesia 5* Heidelberg: Verlag Fur Medizin Dr. Ewald Fischer GmbH, 1988; 138–48

3 American Heart Association. Guideline 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: Advanced Cardiovascular Life Support. Section 6: Pharmacology II: Agents to Optimize Cardiac Output and Blood Pressure. *Circulation* 2000; **102**(Suppl I): I-129–135

Topical anaesthesia for cataract surgery

Editor—We read with interest the report by Aziz and Samra comparing the efficacy of anaesthesia obtained using deep topical fornix nerve block anaesthesia with the conventional peribulbar technique.[1] Deep topical nerve block anaesthesia was first described in 1995.[2] It involves placement of local anaesthetic into the conjunctival fornices, from which it can diffuse across the conjunctiva into the peribulbar space and so reach the scleral nerves behind the eye. The authors concluded that this method was a useful needle-free technique for patients undergoing cataract surgery with phacoemulsification.

Local anaesthesia for cataract surgery prevents the metabolic and hormonal changes seen when surgery is performed under general anaesthesia and provides better cardiovascular stability.[3,4] It is unclear whether deep topical nerve block anaesthesia would provide the same degree of metabolic and cardiovascular stability. We have attempted to perform deep topical nerve block anaesthesia as described by the authors as we were interested in the efficacy of the anaesthesia obtained, as well as the magnitude of the hormonal response, compared with a conventional peribulbar technique. We were, however, unable to duplicate Aziz and Samra's methodology which consisted of placing two 2×3 cm sponges soaked with bupivacaine deep into the conjunctival fornices. Attempted placement resulted in such distress and discomfort in 10 patients, that the procedure was abandoned. Insertion of smaller sponges was also uncomfortable for the patient and resulted in totally inadequate analgesia and anaesthesia in a further six patients. We have decided not to continue with this practice as we consider there is a risk of causing trauma to the globe or a corneal abrasion. We appreciate that a needle-free technique is inherently safer than a conventional peribulbar injection in avoiding the risks of perforation and haemorrhage, but with an experienced anaesthetist, peribulbar block has a low complication rate and ensures analgesia and akinesia.[5] Inadequate analgesia can lead to patient discomfort and possible movement intraoperatively, thereby increasing the risk of trauma to the eye.

We consider that, at present, deep topical nerve block anaesthesia is an unproven and potentially unsafe method of providing anaesthesia for cataract surgery.

G. Nicholson
C. Mantovani
G. M. Hall
Department of Anaesthesia
St George's Hospital Medical School
London

1 Aziz ES, Samra A. Prospective evaluation of deep topical fornix nerve block *versus* peribulbar nerve block in patients undergoing cataract surgery using phacoemulsification. *Br J Anaesth* 2000; **85**: 314–6

2 Rosenthal KJ. Deep, topical nerve-block anaesthesia. *J Cataract Refract Sur* 1995; **21**: 499–503

3 Barker JP, Vafidis GC, Hall GM. Postoperative morbidity following cataract surgery. A comparison of local and general anaesthesia. *Anaesthesia* 1996; **51**: 435–7

4 Barker JP, Vafidis GC, Robinson PN, Hall GM. Plasma catecholamine response to cataract surgery: a comparison between local and general anaesthesia. *Anaesthesia* 1991; **46**: 642–5

5 Davis DB, Mandel MR. Efficacy and complication rate of 16,224 consecutive peribulbar blocks. *J Cataract Refract Surg* 1994; **20**: 327–37

Editor—We welcome the opportunity to respond to Drs Nicholson, Mantovani and Hall. The point they raised regarding the size of the sponge we used is unfortunately a typographical error as it is 2×3 mm and not 2×3 cm. We apologize for not noticing this error sooner, which could have avoided any confusion.

In our method,[1] after applying local anaesthetic drops to the conjunctiva, we used a 2×3 mm segment cut from the tip of MICROSPONGE™(regular tip) (Alcon®surgical, Alcon Laboratories, Inc., Fort Worth, TX, USA) soaked in local anaesthetic. soaking the sponge in this way will cause its size to double. Using bigger segments will encroach on the cornea and lead to discomfort; we did not receive any such complaints from our patients. The size of the sponge should be adjusted according to the depth of the fornices. in some patients with deep fornices one could even use a 3×4 mm sponge (personal communication, J. Rosenthal).

Regarding the safety of the technique, as in previous studies,[2 3] we had no complications. We also have to stress that deep topical fornix nerve block anaesthesia (DTFNBA) is only suitable for cataract surgery using phacoemulsification and not for extracapsular cataract extraction surgery as there is no akinesia of the extraocular muscles. DTFNBA needs an experienced surgeon as the eye wil be moving during surgery, but after a definite surgical learning curve the procedure can be performed with miminal patient discomfort. Surgical training and patient preparation are the key to safe use of DTFNBA.

We believe that DTFNBA is very suitable for patients undergoing cataract surgery with phacoemulsification, especially those on anticoagulants and those who will not accept the use of injections around the eye.

E. S. Aziz
Department of Anaesthesia
Cairo University
Egypt

A. Samra
Department of Ophthalmology
Research Institute of Ophthalmology
Cairo
Egypt

1 Aziz ES and Samra A. Prospective evaluation of deep topical fornix nerve block *versus* peribulbar nerve block in patients undergoing cataract surgery using phacoemulsificatio. *Br J Anaesth* 2000; **85**: 314–6
2 Rosenthal KJ. Deep topical fornix nerve block anaesthesia. *J Cataract Refract Surg* 1995; **21**: 499–503
3 Bhupendra CK Patel, Thomas E, *et al.* Prospective evaluation of topical versus retrobulbar anaesthesia: a converting surgeon's experience. *J Cataract Refract Surg* 1998; **24**: 853–60

Eye dimension and inadvertent perforation during eye blocks

Editor—We read with interest the article by Vohra and Good evaluating the dimensions of the eyeball as risk factors for inadvertent perforation during eye blocks.[1] The three main features of this work are that: (i) in myopic eyes, the axial length is more increased than the equatorial horizontal width; (ii) myopic staphylomas are only present in myopic eyes, and most frequently in very highly myopic eyes (axial length >29 mm); and (iii) that myopic staphylomas are often located inferiorly, and never at the equator. The authors conclude that the medial canthus approach should theoretically be safer than the inferolateral approach for peribulbar anaesthesia, and that biometry (axial length measurement of the eyeball) is not sufficient to localize staphylomas.

It has long been admitted that the main risk factor for perforation is severe myopia (i.e. axial length of the globe greater than 26 mm). Regarding Vohra and Good's conclusions, myopic staphyloma should be the only risk factor for perforation and severe myopia should act only as a confounding factor, because it is frequently associated with staphyloma. Indeed this has accurately been confirmed in a survey on 50 000 eye blocks[2]: myopia without staphyloma is not a risk factor for inadvertent perforation.

We have drawn the needles in place for retrobulbar, inferolateral peribulbar, and medial canthus peribulbar blocks in three eyes with varying dimensions as described by Vohra and Good (Figure 1). it is clear that retrobulbar block should theoretically increase the risk of perforation. In the medial canthus block, peribulbar block with deep insertion of the needle into the orbit and an angulation towards the globe are avoided, a fact that should increase its safety margin.

Vohra and Good note that poor technique or lack of physician experience may cause a problem. This highlights the fact that anaesthetists need to be educated more about eye blocks.[3] They must be aware of abnormal globe dimensions and of the existence of staphyloma before performing eye blocks. Performing biometry before an eye block in all myopic eyes—even if not required for surgery—has been proposed.[4]

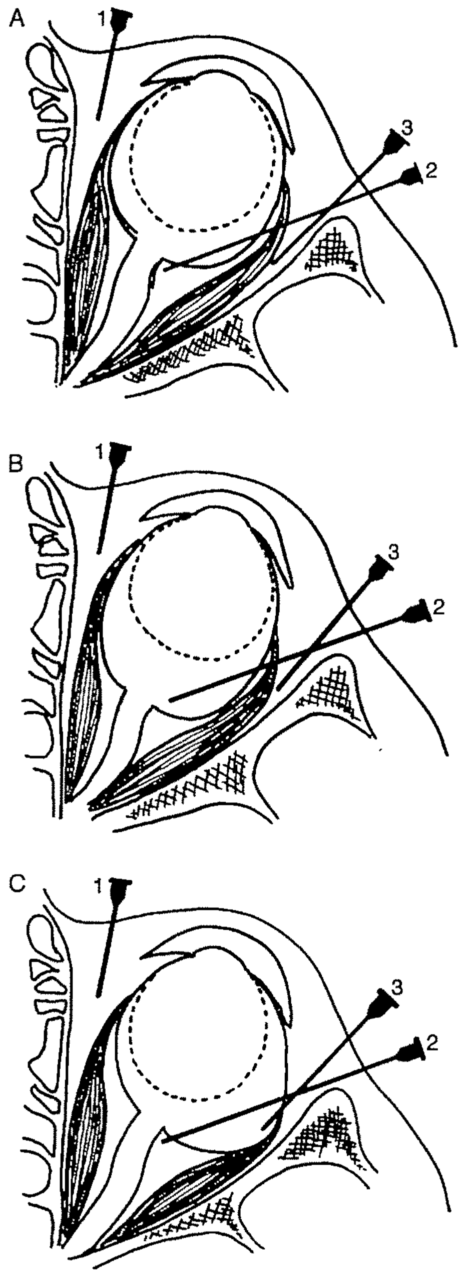

Fig. 1. Schematic view of three eyes with needles in position. Dotted lines show outline of normal (non-myopic) eye. (A) severe myopia without staphyloma; (B) posterior staphyloma; (C) inferolateral staphyloma. Needles: 1 = medial canthus peribulbar block; 2 = retrobulbar block; 3 = inferolateral peribulbar block. Note that only the position of needle 1 does not risk perforation.

We agree that all severely myopic patients should have two-dimension B scan echography pre-operatively for anaesthetic purposes only.

Our only point of disagreement with Vohra and Good is the confusion they have produced between two different techniques. Medial canthus compartment block is *peribulbar* anaesthesia.[5,6] It may be used as a single injection or accompanying a retrobulbar or inferotemporal peribulbar injection. The technique we described is medial canthus *episcleral* (sub-Tenon's) anaesthesia.[7–10] The needle is introduced nearer to the globe, but tangentially to the sclera, which should prevent perforation. The episcleral space guides the spread of local anaesthetic around the globe—this explains the good sensory block we obtain—and into the rectus muscle sheath, producing good akinesia. This technique appears to provide more constant akinesia than classical inferotemporal anaesthesia.[11] in our unpublished experience of about 4000 patients including myopic eyes with an axial length up to 34 mm, no perforation occurred.

Jacques Ripart
Emmanuel Nouvellon
Jean-Jacques Eledjam
Départment Anesthesie-Douleur
Centre Hospitalier Universitaire
Nimes
France

1 Vohra SB, Good PA. Altered dimensions of axial myopia as risk factor for penetrating injury during peribulbar anaesthesia. *Br J Anaesth* 2000; **85**: 242–5
2 Edge R, Navon S. Scleral perforation during retrobulbar and peribulbar anesthesia: risk factor and outcome in 50 000 consecutives injections. *J Cataract Refract Surg* 1999; **25**: 1237–44
3 Kleinman B, Perlman JI, Anderson C, Frey K, Stevens RA, Belusko R. A collaborative regional ocular anesthesia training program: successes and failures. *J Clin Anesth* 1999; **11**: 301–4
4 Boase DL. Local anaesthesia revisted. *Eye* 1996; **10**: 531–2
5 Churchill AJ, James TE. Should myopes have routine axial length measurements before retrobulbar or peribulbar injection. *Br J Ophthalmol* 1996; **80**: 498
6 Hustead RF, Hamilton RC, Loken RG. Periocular local anesthesia: medial orbital as an alternative to superior nasal injection. *J Cataract Refract Surg* 1994; **20**: 197–201
7 Brahma AK, Pemberton CJ, Ayeko M, Morgan LH. Single medial injection peribulbar anaesthesia using prilocaine. *Anaesthesia* 1994; **49**: 1003–5
8 Ripart J, Metge L, Prat-Pradal D, Lopez FM, Eledjam JJ. Medial canthus single injection episcleral (sub-tenon) anesthesia computed tomography imaging. *Anesth Analg* 1998; **87**: 43–5
9 Ripart J, Prat-Pradal D, Charavel P, Eledjam JJ. Medial canthus single injection episcleral (sub-Tenon) anesthesia anatomic imaging. *Clinical Anatomy* 1998; **11**: 390–5
10 Ripart J, Lefrant JY, L'Hermite J, *et al.* Caruncle single injection episcleral (sub-tenon) anesthesia for cataract surgery: mepivacaine versus a lidocaine-bupivacaine mixture. *Anesth Analg* 2000; **91**: 107–9
11 Ripart J, Lefrant JY, Vivien B, *et al.* Ophthalmic regional anesthesia: medial canthus episcleral (subtenon) anesthesia is more efficient than peribulbar anesthesia. A double blind randomized study. *Anesthesiology* 2000; **92**: 1278–85

Editor—Thank you for the opportunity to reply to Ripart, Nouvellon and Eledjam. We appreciate that they agree with most of our views, however they have raised some points which we would like to clarify. First, our paper does not suggest that myopic staphylomas are never present at the equatorial region, just that none was present in the axially myopic eyes studied.[1]

Second, Ripart and colleagues quote the survey by Edge and Navon[2] and conclude that axial myopia without staphyloma is not a risk factor for scleral perforations. In this interesting survey, staphyloma was the only identifiable predisposing factor associated with the inadvertent perforations observed in the axially myopic eyes. However, the authors of the survey also suggest that the number of inadvertant injuries would have been higher had myopia *per se* been a risk factor.

There have been many reports of perforations occurring in eyes presenting with a wide range of axial myopia as well as in normal eyes.[3–6] It is unlikely that all those axially myopic eyes were staphylomatous. The low number of injuries in the survey[2] probably points to the fact that ever since the dangers of axial myopia were first highlighted, the operators have been extra careful in their technique of injection, the angle of insertion, and the choice of length of needle. With reference to Figure 1A in Ripart's letter, it is not difficult to visualize that a misjudged angulation towards the globe during a peribulbar injection using the infero-temporal approach in an axially long eye could result in an injury. In our opinion, therefore, it would be imprudent to dismiss simple myopia as a risk factor. Until firm scientific evidence is available, it would be wise to err on the side of caution.

We would like to reiterate the statement that *the axially myopic eye is at risk of perforation due to elongation of the globe and this risk is further* ***increased*** *due to the likelihood of co-existing inferior posterior staphyloma, especially during infero-temporal injection.* There is no room for complacency when performing eye blocks, even though they appear to be technically easy. The potential complications of poor technique are devastating. The need for training and thorough understanding of the anatomical abnormalities of the globe cannot be over-emphasized. To this end, we have already indicated the need for *B* scan echography in addition to biometry for these patients in our article.[1]

We accept that the technique described by the Ripart owes its success to the episcleral spread of the injectate.[7] The successful single medial injections performed at the caruncle are not dissimilar to their own technique though the finer details and descriptions may vary slightly.

S. B. Vohra
P. A. Good
Department of Anaesthesia and Birmingham and Midland Eye Centre
City Hospital NHS Trust
Birmingham
UK

1 Vohra SB, Good PA. Altered globe dimensions of axial myopia as risk factors for penetrating ocular injury during peribulbar anaesthesia. *Br J Anaesth* 2000; **85**: 242–5
2 Edge R, Navon S. Scleral perforation during retrobulbar and peribulbar anesthesia: risk factors and outcome in 50 000 consecutive injections. *J Cataract Refract Surg* 1999; **25**: 1237–44
3 Hay A, Flynn HW, Hoffman JI, Rivera AH. Needle penetration of the globe during retrobulbar and peribulbar injections. *Ophthalmology* 1991; **98**: 1017–24
4 Duker JS, Belmont JB, Benson WE, *et al.* Inadvertent globe perforation during retrobulbar and peribulbar anesthesia. *Ophthalmology* 1991; **98**: 519–26
5 Wearne MJ, Flaxel CJ, Gray P, Sullivan PM, Cooling RJ. Vitreoretinal surgery after inadvertent globe penetration during local ocular anesthesia. *Ophthalmology* 1998; **105**: 371–6
6 Grizzard WS, Kirk NM, Pavan PR, Antworth MV, Hammer ME, Roseman RL. Perforating ocular injuries caused by anesthesia personnel. *Ophthalmology* 1991; **98**: 1011–6
7 Ripart J, Prat-Pradal D, Vivien B, Charavel P, Eledjam JJ. Medial canthus episcleral (sub-Tenon) anesthesia imaging. *Clin Anat* 1998; **11**: 390–5

Safe placement of central venous catheters

Editor—Cupitt[1] asks us to consider 15 cm central venous catheter (CVC) lines rather than 20 cm lines to reduce the incidence of tip misplacement below the carina. Following articles in the BJA,[2 3] an audit of CVCs inserted prior to admission to our adult general ITU was carried out (lines inserted in the operating theatre, ITU, HDU, wards and other hospitals). Thirty-nine of the 40 non-dialysis lines were 15 cm in length, and one was 20 cm. Of the 31 right-sided insertions, 15 had tips lying in the SVC/atrium below the level of the carina (one to 75 mm). If the tip position was adjusted for a theoretical 12cm line then seven of the 31 would still have been below the carina (assuming the same skin positioning). Of the eight non-dialysis CVCs inserted *via* the left side six had tips in the SVC/atrium and two had tips in the innominate vein. Three of these six in the SVC/atrium were below the carina. But it is difficult to judge the impact of shorter left-sided lines on final positioning.

Fifty-five per cent of all our catheters (standard and dialysis) failed to pass the criteria that the tip lay above the carina, with no evidence that the tip abutted a vessel wall. This was an especially difficult test for left-sided insertions (9/13 failing). Catheters judged to be inappropriately positioned by these criteria were unlikely (4/26) to have been repositioned on a repeat CXR taken within 36 h.

Thus, 15 cm lines alone are unlikely to solve the problem of line tip position. Simple subtraction of 30 mm from the positions obtained in this audit suggests that 12 cm lines (which are available) would be more promising for right-sided insertions. Whatever length is used it is only necessary to insert the line to a distance that ensures that the proximal orifice will not accidently enter the subcutaneous tissues: a technique is suggested by Chalkiadis and Goucke.[4] For left-sided lines, perhaps positioning in Fletcher and Bodenham's Zone A[2] is the best compromise, and a 15 to 20 cm line appropriate.

Importantly, there appeared a reluctance to reposition a fixed line which is functioning well based on the post-insertion CXR. To encourage this, it may be appropriate to delay suturing of the line until the post-insertion CXR is obtained.

J. M. Crawford
Department of Anaesthesia
Western Infirmary
Glasgow
UK

1 Cupitt JM. Safe placement of central venous catheters. *Br J Anaesth* 2001; **86**: 291
2 Fletcher SJ, Bodenham AR. Safe placement of central venous catheters: where should the tip of the catheter lie? *Br J Anaesth* 2000; **85**: 188–91
3 Schuster M, Nave H, Piepenbrock S, Pabst R, Panning R. The carina as a landmark in central venous catheter placement. *Br J Anaesth* 2000; **85**: 192–4
4 Chalkiadis GA, Goucke CR. Depth of central venous catheter insertion in adults: an audit and assessment of a technique to improve tip position. *Anaesth Intensive Care* 1998; **26**: 61–6

Editor—Crawford's study is interesting. The simple crux of the matter is that (at least for right-sided insertions) we should be using shorter catheters, whether they be 12 cm or 15 cm or any other dimension. One could argue that the shorter the better so long as the lumen orifices, including the tip, lie within the vein. We should be aiming for optimum tip position, no redundant loops of catheter, and secure fixation.

The problem with left-sided insertions is more difficult and I do not think the solution is as straightforward. I have to disagree with Crawford. He suggests that Fletcher and Bodenham's Zone A[1] is the best compromise using 15 to 20 cm catheters. I think the chance of successful and safe tip placement in Zone A is significantly less than in Zone C (innominate vein). As Fletcher and Bodenham state, Zone C represents a suitable site for left-sided insertions and, in my opinion, would be more easily attainable with shorter catheters.

We must not forget that the catheters are intended to be intravenous, not intracardiac.

J. M. Cupitt
Blackpool Victoria Hospital
Lancashire
UK

1 Fletcher SJ, Bodenham AR. Safe placement of central venous catheters: where should the tip of the catheters lie? *Br J Anaesth* 2000; **85**: 188–91

The time has come for non-interchangeability of spinal and epidural equipment with intravascular access ports

Editor—Two recent tragedies in the UK resulting in patient death have involved the administration of drugs via an unintended route. One incident involved the placement of vincristine into the subarachnoid space rather than the intended intravenous route, the other injection of bupivacaine intravenously, rather than the intended epidural route. These errors have devastating consequences for the physicians involved, despite the recognition that error is a fundamental human trait.[1] All anaesthetists will be aware of how close they have come to committing similar errors during their practice.

The inherent problem is the interchangeability of spinal and epidural equipment with that of intravascular access ports. Minimizing this risk involves introduction of non-interchangeability of equipment between the two routes of drug administration. This could be achieved by altering the calibre of the connection ports on all equipment intended for spinal or epidural use to a new standard size. This size should be wider than on intravascular connection ports and similar to that which exists for scavenging and breathing systems. There would be an additional cost of converting and maintaining the new system but this is justified, especially in the light of the £25 million per annum provision for single-use surgical equipment for tonsillectomy throughout the NHS which minimizes the theoretical risk of transmission of variant Creutzfeldt-Jacob disease.

Dr David Laws
Department of Anaesthesia
Sunderland Royal Hospital

1 Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is human. Building a Safer Health System.* Washington: National Academy Press, 1999

Fault after cannulation with a Y can

Editor—Figure 1 shows a photograph of a recent fault found after annulation with a Y can (SIMS, Smiths Industries Medical Systems, Colchester, Essex, UK).

Normally following insertion within a vessel, blood flows into the hub (A in Figure 1). The lateral wings (B) are squeezed together, and the hub and needle are removed. In this case, the hub was separate from the needle, leaving the needle within the patient (C). As this was unsatisfactory, the whole unit was removed from the patient; a further cannulation was successful.

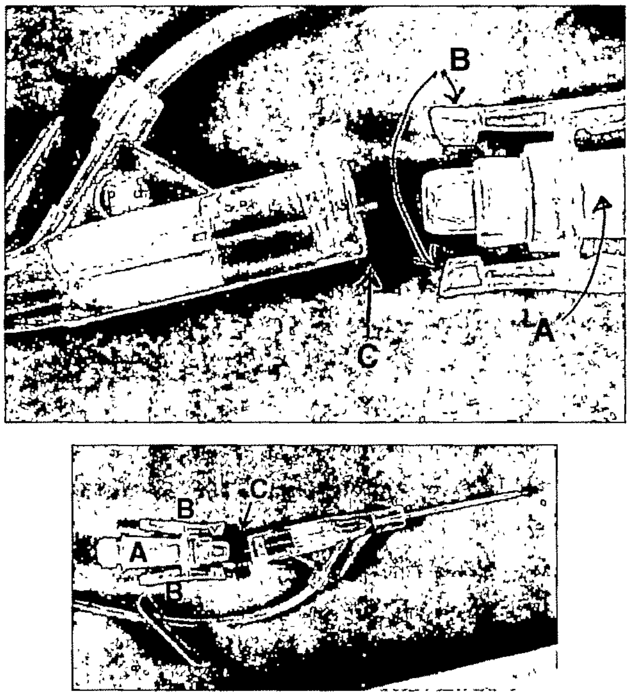

Fig. 1. Fault in a Y can found after cannulation.

The incident was reported to SIMS, who considered it to be an isolated incident, and not a batch-related problem. No corrective action was felt appropriate by the manufacturer.

D. V. A. Morle
Hartlepool
UK

British Journal of Anaesthesia **86** (6): 905–908 (2001)

Book Reviews

Bonica's Management of Pain, 3rd Edn. John D. Loeser (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 2178; indexed; illustrated. Price US$259. ISBN 0-683-30462 3.

Management of Pain appeared first in 1953 when John Bonica began to popularize the use of nerve blocks in the diagnosis and treatment of pain syndromes. It was a seminal work and so complete that the second edition was not published until 1990. That edition was expanded and more comprehensive. Expansion has continued with the publishing of the third edition, which has a total of four editors and 132 contributing authors. The book still contains a lengthy contribution from Dr Bonica who is now 83 years old.

Bonica's Management of Pain has become a huge encyclopaedic work of more than 2000 pages—the postage alone would have bought a small paperback–and it costs a not inconsiderable $259. For your money, however, the whole field of pain management as it is currently seen from Seattle is laid at your feet. Almost all of the contributors come from the University of Washington School of Medicine and this has allowed close editing, elimination of repetition, good cross-referencing within the book, and a generally cohesive approach. Chapters have been written quickly, permitting inclusion of references up to 1999. All the chapters are extensively referenced.

The book is divided into five parts, each of which would stand alone as a book (and given the physical dimensions of this work there is a good argument to produce it as a series of more handy volumes). These sections are devoted to: 'Basic Considerations of Pain', 'Evaluation of the Pain Patient', 'Generalized Pain Syndromes', 'Regional Pains', and 'Methods for Symptomatic Control'. Each of these sections is remarkably comprehensive with great attention paid to the whole patient. There are even paragraphs devoted to the legal and industrial aspects of compensation for painful injuries.

The introduction to the book starts weakly with an historical résumé, which would have been written better by a historian, but then moves on to an interesting passage discussing reasons for failure of pain control. This is the crux of the problem and should perhaps have been the start of the book.

Parts two and three deal with evaluation of the pain patient and generalized pain syndromes and here the complete breadth of the book becomes apparent as psychiatrists, behavioural psychologists and specialists in rehabilitation medicine all contribute useful text. Each chapter ends with a brief summary which depressingly often concludes that 'too little is known... no line of treatment can be recommended'.

The part considering regional pain divides the body up into areas: upper limb, head, abdomen, pelvis and perineum, back and lower limb, and the structure of each section is similar. Each begins with a thorough review of the regional anatomy—in practice, duplicating standard anatomy texts—and then has an extensive table of differential diagnosis before going on to consider pains in great detail. At first sight the tables resemble a faultfinding chart supplied with a new washing machine, but in use, are so comprehensive that scanning them would ensure that no possible diagnosis was overlooked. Each table then provides cross-references to the appropriate chapter for further information. Throughout the book, great care is taken to use standardized nomenclature in order to ensure that different studies can be compared. But the overall style is slightly ponderous and lacks the conciseness and clarity of say, the *Drug and Therapeutics Bulletin.*

Part five considers methods available for symptomatic control and includes all methods currently available for the treatment of pain, with extensive sections on psychological techniques, physiotherapy, implanted electrical stimulators, and multidisciplinary approaches to pain management.

This then is an astonishing book for its comprehensive cover of every pain situation and virtually every aspect of that pain. Experts in pain therapy will know some of this material but by no means all. It stands as the current state-of-play in this field and, as it were, a datum point from which knowledge can advance. There is the enduring question of whether such books are needed in the electronic age, but there is a virtue in compressing all knowledge up to this point and displaying it. Less considered and more up-to-date information can be found elsewhere but when faced with a patient with refractory Sudek's atrophy there is no more comprehensive source of information available to the clinician. Unfortunately, the section will conclude that 'too little is known ... and no one line of treatment can be recommended'!

A. B. Loach
Oxford

Analgesia, Anaesthesia and Pregnancy—A Practical Guide. S. M. Yentis, D. Brighouse, A. May, D. Bogod and C. Elton. Published by Saunders (Harcourt Publishers Ltd), London. Pp. 402; indexed; illustrated. Price £45. ISBN 0-7020-2322 1.

This 'practical' guide is less of the technical 'know how to do' analgesia and anaesthesia in pregnancy, and more of the description of the formatted lay-out of text. The book is divided at almost every other page into a series of topics chosen by the authors. In all, there are 166 topics. The topics are organied into sections: preconception, pregnancy, puerperium and organizational aspects, closely fulfilling the expectations of the book's title. Each topic is succinctly described in two to four pages using written text with recurring headings of 'problems' and 'management options', particularly for clinical topics. The text is supplemented by figures, tables and references.

The authors, Drs Yentis, Brighouse, May, Bogod and Elton, have targeted a number of readers such as examination candidates and specialist anaesthetists working in obstetric anaesthesia. For examination candidates, the physiology of pregnancy and aortocaval compression is adequate for the Primary FRCA. References are limited in number and often are reviews rather than definitive studies. The topic of placental transfer of drugs, for example, has no references and local anaesthetics are considered only from a British point of view. Basic knowledge of drugs is assumed but the index comprehensively lists the important drugs and where they are mentioned in the text. Topics specifically related to drugs and pregnancy, such as breast feeding and midwives' use of drugs, are included in the later sections.

For clinicians, the evidence-base for labour ward management is presented in the section on organizational aspects where methodological weaknesses in research are also described. There is no mention of the Cochrane Collaboration which has provided systematic reviews and a sound evidence basis for many obstetric issues. Other organizational aspects such as consent, medicolegal problems and records will be of interest to the practising clinician. These topics are also tested in the FRCA and certainly at interviews for the aspiring consultant obstetric anaesthetist.

Answers to basic clinical questions, such as how to examine a pregnant woman and what specific information should be given prior to epidural analgesia in labour, are not easy to locate in the

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text. Almost a third of the book relates to problems not confined to obstetrics. This part contains 59 topics ranging from coarctation of the aorta to steroid therapy. The authors agree that it has been difficult to classify these topics. Where possible they are in random systematic order rather than what would seem at first glance to be an easier approach, that of alphabetical order.

The diversity of topics and their limited analysis makes it easy to read the text quickly and pick up key points. At the end of each topic is a bullet point synopsis. This repetition reinforces those features of the subject considered pertinent by the authors and are essentially qualitative statements. It is these characteristics of the book that create the practical approach. It is certainly not a technical document but seeks to present bite size pieces of information around the whole experience of obstetric anaesthesia, with descriptions of most of the medical conditions we face in an increasingly elderly population of mothers.

The book may not answer all the questions for the examinations or provide in depth knowledge but it is certain to be popular given its broad authorship and succinct style.

A. Holdcroft
London

Problems in Anaesthesia; Cerebral Protection, Resuscitation and Management. Volume 12 number 4, October 2000. C. K. Spiss (guest editor), L. A. Fleisher, D. S. Prough (editors in chief). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 121; indexed, illustrated. ISSN 0889-4698.

This small book, from the *Problems in Anaesthesia* series, comprises 121 pages and perhaps inevitably presents a somewhat American perspective on various monitoring techniques currently available in neuroanaesthetic and neurointensive practice and in the management of brain trauma, despite having some expert European authors.

The book has 11 chapters which are summarized in an initial contents section. Each chapter is referenced at its conclusion, and there is a comprehensive subject index at the end of the book. The volume can be considered in three sections according to subject material. The first three chapters cover cerebral physiology and pathophysiology. While there is little new information here, and some authors have used considerable space to present their own research, the data presented is generally comprehensive and well referenced. However, most of the research presented is explanatory and therefore provides sparse clinical material to influence anaesthetic practice. A later chapter concerning neuronal death and pharmacological interventions (including anaesthetic agents), and another on the effects of anaesthetics on cerebral flow and metabolism, appear 'out of place' and might have integrated better by earlier placement.

The middle chapters of the book concentrate on monitoring techniques including cerebral oxygeneration, electrophysiology, intracranial pressure measurement and transcranial Doppler ultrasonography. Although some of these subjects are by no means fully covered, they are well referenced and would be an excellent starting source of material for those not familiar with these techniques. They also set the tone for the last section of the book. This deals predominantly with brain trauma management. It presents a comprehensive overview of intracranial pressure management, although the reader could be forgiven for believing that the concept of targeted intracranial pressure therapy was an American idea based on recommendations from the Brain Trauma Foundation! While 'Lund' therapy is discussed in brief, the reader will be left with little overall concept of how intracranial pressure and cerebral perfusion pressure is managed in Europe; nor is there substantial discussion about the lack of evidence for ICP therapy in clinical practice. Peri-operative fluid management in patients with intracranial hypertension is comprehensively reviewed while hypotheramia is given realistic appraisal by the chapter's Austrian authors.

I was generally impressed by the standard of writing of this little book although many chapters would have been improved by illustrations, especially those describing monitoring equipment. The merits of the book are the honesty which appears in several chapters regarding the value of therapeutic interventions previously endorsed enthusiastically without realistic substantiation, and a recognition of the lack of good pragmatic trials to justify many current intensive care practices. On the negative side, some sections devote excessive space to the authors' own work leading to imbalance or omission, and some chapters are biased towards parochial research literature. Portions on monitoring occasionally fail to emphasize current prevalence and usefulness of techniques in a clinical setting.

In summary, most of the information in this book can be found more comprehensively and critically reviewed in larger specialist text books. In the preface, Christian Spiss the guest editor emphasizes that this issue 'is intended to give an updated overview of the latest scientific developments and current points of view'. Overall, I believe that this publication meets these standards and in this regard Spiss is to be congratulated.

N. M. Dearden
Leeds

Problems in Anesthesia: PACU and Anesthetic Management. Sherif Afifi, Stanley Rosenbaum, Lee A. Fleisher and Donald S. Prough (editors). Published by Lippincott, Williams and Wilkins, Hagerstown. Pp. 352; indexed. Price US$56. ISSN 0889-4698.

This small, multi-author book gives an excellent, clear and concise overview of common problems encountered in the perioperative period. It emphasizes how a smooth recovery from surgery and anaesthesia is becoming increasingly important in a climate where early discharge and rapid patient turnover are necessary to satisfy economic targets without compromizing the quality of care.

The book is well laid out in short chapters dealing with specific physiological problems, with a final chapter about scoring systems and their limitations. As with most multi-author publications, some chapters are better than others.

The first chapter on post-operative respiratory failure shows how a thorough pre-operative assessment and knowledge of the surgery proposed can predict many post-operative problems. Changes in respiratory function associated with age, body habitus and coexisting disease are discussed, and there are some specific parameters quoted to allow pre-operative optimization in high-risk groups. Problems specific to cardiothoracic and high abdominal surgery are delineated, but the principles can be applied to all patients, with the overwhelming message being prevention of problems by modifying risk pre-operatively.

The chapter on cardiovascular complications covers the problems of myocardial ischaemia and infarction, atrial fibrillation and venous thrombosis in the perioperative period. All sections are excellent with information on prediction and risk factors and advice on intra- and post-operative prevention and management. Although the American Heart Association flow chart looks complicated, the underlying message is clear—that cardiological investigations and opinions should be sought pre-operatively so allowing optimal peri-operative care for the patient.

The chapter on problems with analgesia covers assessment of pain and the consequences of inadequate analgesia, as well as treatment options. Some of the drugs described are not available or in common usage in the United Kingdom, and some of the problems of central neuraxial blockade post-operatively are more relevant to North American ambulatory care than to most British practice. Unfortunately, the use of epidural clonidine is not discussed, presumably because clonidine is not yet approved for this use in North America. As local anaesthetic techniques are discussed, this chapter could to my mind have been linked to the one on recovery from regional anaesthesia. Unfortunately, the latter chapter suffers from tables which are too long and complex to be easily assimilated and the text is somewhat difficult to read. At times, it strays from the remit of the book. However, the table summarizing the American Society of Regional Anaesthesia consensus statements regarding anticoagulants and neuraxial anaesthesia is a comprehensive overview, which answers most of the queries and worries raised by anyone performing epidurals.

The chapter on post-operative nausea and vomiting is excellent, being clear and easy to read. It comprehensively covers the aetiology, treatment and prevention of what is often the most distressing side-effect of surgery for patients.

The chapter on metabolic diseases highlights the issues associated with surgically induced hormonal changes, thermoregulation and fluid administration. Owing to the vast scope of these problems, the commonest have been selected and their aetiologies discussed—glucose problems, changes in corticosteroids, calcium and sodium balance, acid base balance and the problems of hypothermia. The authors stress the importance of clinical vigilance as severe metabolic derangement may not be immediately apparent following anaesthesia. The problems related to temperature control are particularly well covered.

The other chapters are of an equally high quality. All are referenced with recent publications providing up-to-date thought on how to minimize problems in the recovery room and improve patient satisfaction and outcome. This book would be useful to all those involved in recovery room care, both nursing and medical staff.

Jane Beattie
Liverpool

Fibreoptic Intubation. Neil Hawkins and Andrew Dyson. Published by Greenwich Medical Media Limited, London. Pp. 81; indexed; illustrated. ISBN 1-84110-060-9.

This is a first edition book, written by two authors, which is sponsored by Pentax. The book has 83 pages divided into nine chapters, four appendices and a glossary. It is well illustrated and comes with a free CD-ROM disk. The disk provides clips of techniques described in the book, and features views, which illustrate key concepts. It is intended as an introduction to fibreoptic laryngoscopy and intubation, and meant to cover the main areas necessary to enable a beginner to use the scope successfully.

It is a concise and appealing book, which is easy to read and assimilate. The chapters are short and are accompanied by many illustrations. The contents are highlighted at the beginning of each chapter. The first two chapters cover the benefit of having a fibreoptic scope in an anaesthetic department, the history of the scope, its physics, components and handling. The latter is described in a logical order and in easy to understand steps. The book has chapters on the indications and contraindications of fibreoptic intubation for anaesthetized and awake patients using the nasal or oral route, and local anaesthesia of the upper airway. These are standard and essential reading as they contain plenty of hints and aids for the beginnner. The advantages and disadvantages of each technique are well covered and I like the recommendation to intubate awake patients in the seated position. It is my routine practice. Endoscopists sometimes choose what is easy for them, not what the patient prefers. Also, the section on the use of teaching aids and camera equipment is helpful.

Throughout the book, there is plenty of practical advice to facilitate a successful fibreoptic intubation. In the chapter on the conduct of intubation, pre-operative assessment and preparation of patients are dealt with clearly with a description of some emergency and paediatric cases. The value of the simple approach and monitoring are highlighted. Complications of fibreoptic intubation are included in another chapter. The book contains a 'tricks and tips' chapter on how to keep the airway clear and be a successful endoscopist. It also highlights the value of having a second operator during a difficult intubation. This chapter covers many of the problems an endoscopist faces, and gives tips on how to solve them. The final chapter deals with teaching issues. It stresses modern practices and the following of the General Medical Council guidelines on handling of patients for teaching purposes. Various teaching attachments and photographic equipment are also described.

However, there are a few areas which the book does not cover well. The authors do not highlight mistakes that beginners often make. These include: attempts to twist the insertion tube sideways with the guiding hand, to the right or the left, to view structures; failing to differentiate between the primary and secondary carina; and the use of sedatives and opiates instead of allowing sufficient time for local anaesthesia to work. Also, having had local anaesthesia of the upper airway, patients with excessive secretions, will find it difficult to swallow. To reduce secretions, antisialogogues should be given in the ward not the induction room. Active suction not spitting is an easier way to remove secretions. Asking patients to protrude their tongue helps to move the epiglottis away from the bevel of the tracheal tube and expedites easy railroading of the tube. Moreover, the use of translucent tracheal tubes can be confusing to trainees who may think that the scope is outside when it is still inside the lumen of the tube.

The authors appear to be against the use of inhalation induction in difficult cases, yet they favour intubating patients with an unstable cervical fracture under inhalation induction. I am not sure that this is safer than awake intubation, with in-line stabilization of the neck. For each difficult case, a particular technique of intubation or local anaesthetic administration is preferable. In cervical spine fracture, the technique of choice for local anaesthetic administration is nebulization, which minimizes the coughing and uncontrollable movement of the patient caused by 'spray-as-you-go' or cricothyroid puncture techniques.

The advice on extubating the difficult airway is too brief. An algorithm for extubation would have been very useful. In my view, the biggest weakness of this book is the paucity of references (14, which are mainly books). The references should relate easily to the text, particularly to the massive list of conditions associated with difficult intubation.

The CD-ROM disk, which has 23 clips on fibreoptic intubation, is useful in some parts, especially the clips showing normal anatomy and the oesophageal sphincter. But the clip on laryngeal lift, although it carries a minor warning, may cause some harm.

Installation of the disk was difficult. It needed microsoft video clips files and Intel Indeo-5 video drivers. The program is not user friendly and the clips are small and cannot be enlarged. The video format, although viewable on most computers, does not produce optimal video quality for a given file size. It would have been easier for the reader if it operated as a DVD disk.

This is a useful book, particularly its illustrations. Its contents can be read and seen before handling the scope during a workshop or when teaching on patients, with good results. With some modification to the CD-ROM disk, it could be made very useful indeed. I certainly recommend it to trainees and for teaching, but its value for the experienced endoscopist is limited to the illustrations.

S. M. Mostafa
Liverpool

Statistical Methods for Anaesthesia and Intensive Care. Paul S. Myles and Tony Gin. Published by Butterworth Heinemann, Oxford. Pp. 152; indexed, illustrated. Price £19.99. ISBN 0-75-064650.

The preface of this book states: 'the design of this book is such that anaesthetists, intensivists, and trainees can systematically learn the basic principles of statistics (without boredom or frustration)'. Sadly, it does not live up to this promise.

In approximately 150 pages, the book runs the gamut from basic statistical methods such as the chi-squared and *t*-tests, through to Bayesian analysis and survival analysis. It also includes excursions into evidence-based medicine and clinical-trial design, and a chapter on common statistical errors. The result is that complex issues are frequently skimmed over in a few sentences and the text often lapses into language which will be opaque to the beginner (and perhaps to the more experienced reader as well). For example, in the discussion of degrees of freedom, we are told that: 'the sample mean is a predetermined estimate of the population mean (each individual in the sample is a random selection, but not the fixed sample mean value)'. This statement is not preceded by any discussion of sampling.

The book is didactic on issues where there is considerable disagreement among different authorities. Chapter 10 is uncritical in its advocacy of large clinical trials. Bruce Charlton has pointed out on a number of occasions that, while large clinical trials are an important and powerful tool, this approach is not without problems. Recruitment into large trials is most easily organized in major centres where the condition being studied may be a particular academic and clinical interest and where there is an infrastructure to manage the study. This may lead to the recruitment of an unrepresentative study population. Also, important subgroup effects may be lost in the global effect estimate obtained in the large study population.

In Chapter 12 we are told that: 'placebo controlled studies have very little value …'. Many authorities would disagree with this. Martin Tramer has pointed out that failure to show a difference between a treatment and an active control does not necessarily indicate equivalence. The possible conclusions under these circumstances are: both drugs are equally effective; both drugs are equally ineffective; or the trial design was inadequate to show a read difference between the two treatments.

The book also contains errors of fact. On page 8, the definition given for the rate of an event is in fact the definition of the odds of an event. I suspect that one does not have to be too much of a purist to take exception to the statement on page 22, that the *P* value indicates the likelihood that the result obtained or one more extreme could have occurred randomly by chance assuming that H_0 is true. Under the frequentist model of statistics, this statement is simply not true.

The book is said to be illustrated by examples taken from the anaesthetic and intensive care literature. These examples consist in the main of a table of data presented with little or no explanation and followed by one or two sentences of discussion. They often add little to the understanding of the statistical method being discussed.

I do not feel that this book would be of value to a beginner in statistical methods. If it were better written, it might provide a useful rapid review of statistical methods for a more experienced reader. However, I fear that the errors in the text written in opaque language would lead to such a reader being confused or irritated. I find myself unable to recommend this book.

S. J. Howell
Bristol

All About Anaesthesia. Jan Davies and Rod Westthorpe. Published by Oxford University Press, Melbourne. Pp. 201; indexed; illustrated. Price £7.50. ISBN 0-19-5510895.

This book is a short guide for the lay person to the people and processes involved in anaesthesia. It is written from the perspective of the pre-operative patient. As such, the style is deliberately informal and rather naïve to the extent that some may find it a little patronizing. However, considering the target readership, the content is quite extensive. The anaesthetist is introduced to the reader by a short description of anaesthetic training and examinations, the supervizing bodies and the job role. The book goes on to cover the pre-operative visit, choice of anaesthetic technique, conduct of anaesthesia, monitoring, recovery, post-operative analgesia and discharge home. There is also discussion of the effects of intercurrent illness and the extremes of age. These issues are illustrated by following the stories of seven 'typical' patients undergoing an anaesthetic, covering a range of ages from neonate to the elderly, and a range of anaesthetic techniques including regional anaesthesia. This gives the authors an opportunity to present and answer some 'frequently asked questions' in an indirect manner. The book emphasizes throughout the relative safety of modern anaesthesia, whilst explaining that complications can and do occur.

At the end of the book is an additional section of frequently asked questions ('Common Fears') and a section on complications of anaesthesia. There is a list of suggested questions that patients should ask their anaesthetist, a brief chapter on the history of anaesthesia, and a glossary. There are also web-site references for further reading.

Though quite simplistic in style, this book is probably too long and too involved for the average adult about to undergo an anaesthetic. Most patients should be quite adequately catered for with a good pre-operative visit by their anaesthetist, perhaps with the addition of a short information leaflet. However, this book might be much more appreciated by parents of children requiring general anaesthesia, particularly if repeated anaesthetics may be involved. Particular attention is certainly paid to paediatric anaesthesia, with two of the seven case histories being about children. A number of typical parental concerns and anxieties are addressed in a sympathetic manner. But certainly this book could be recommended to any patient or parent who would like to read more about anaesthesia.

T. M. Cope
Liverpool

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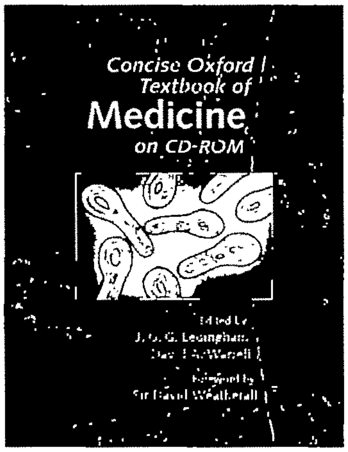

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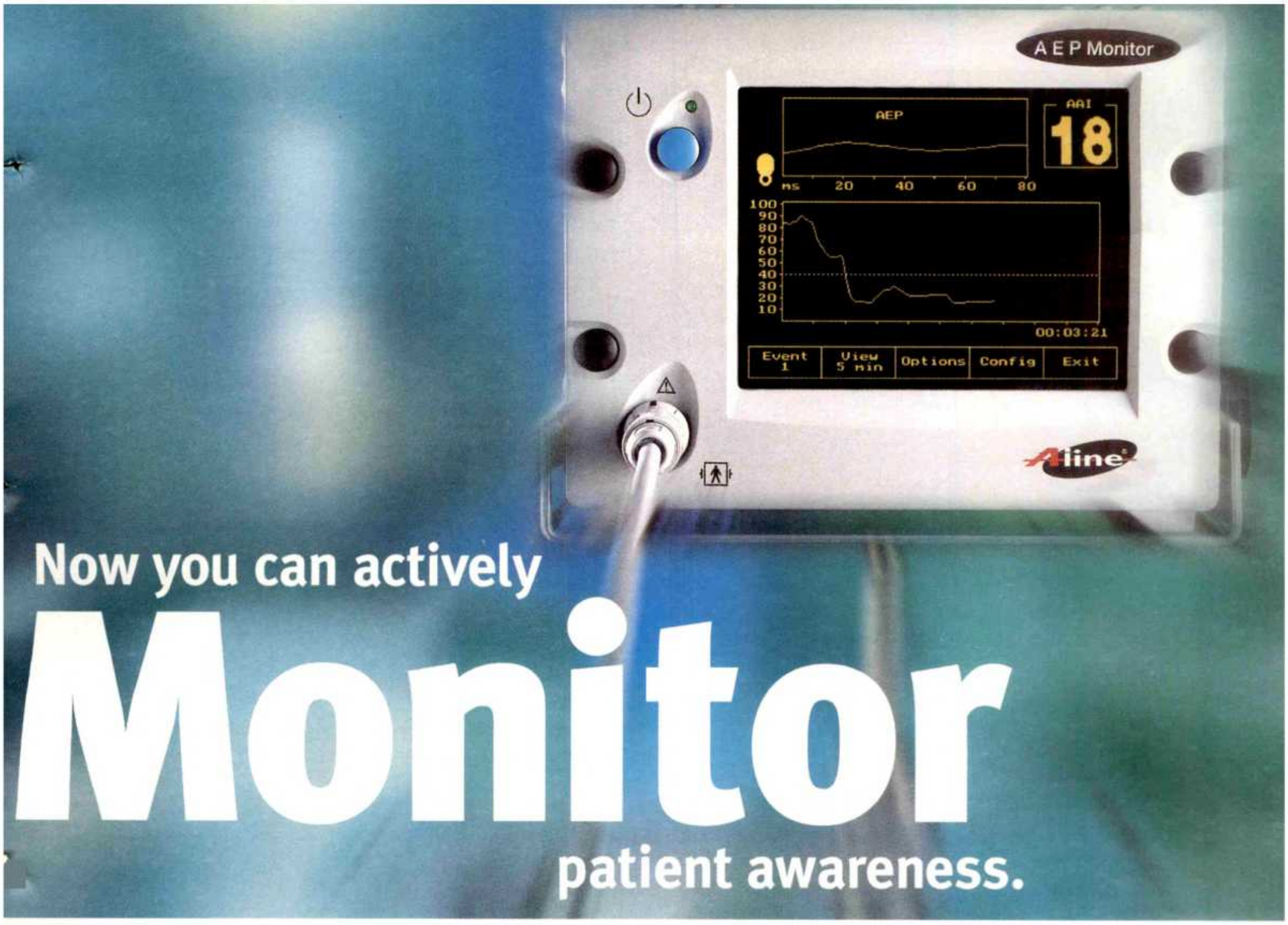

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STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, July 6, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact:
Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: +44 (0) 131 536 3652; Fax: +44 (0) 131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Ventilation Through the Ages

ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

International ventilation conference covering all aspects of respiratory support from neonates through to adulthood.

To be placed on the list for registration details, please contact: Sue Hubbard, ERMEC, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK. Tel +44 (0)1482 674007; Fax: +44 (0)1482 586587; E-mail: suehermec@hotmail.com

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

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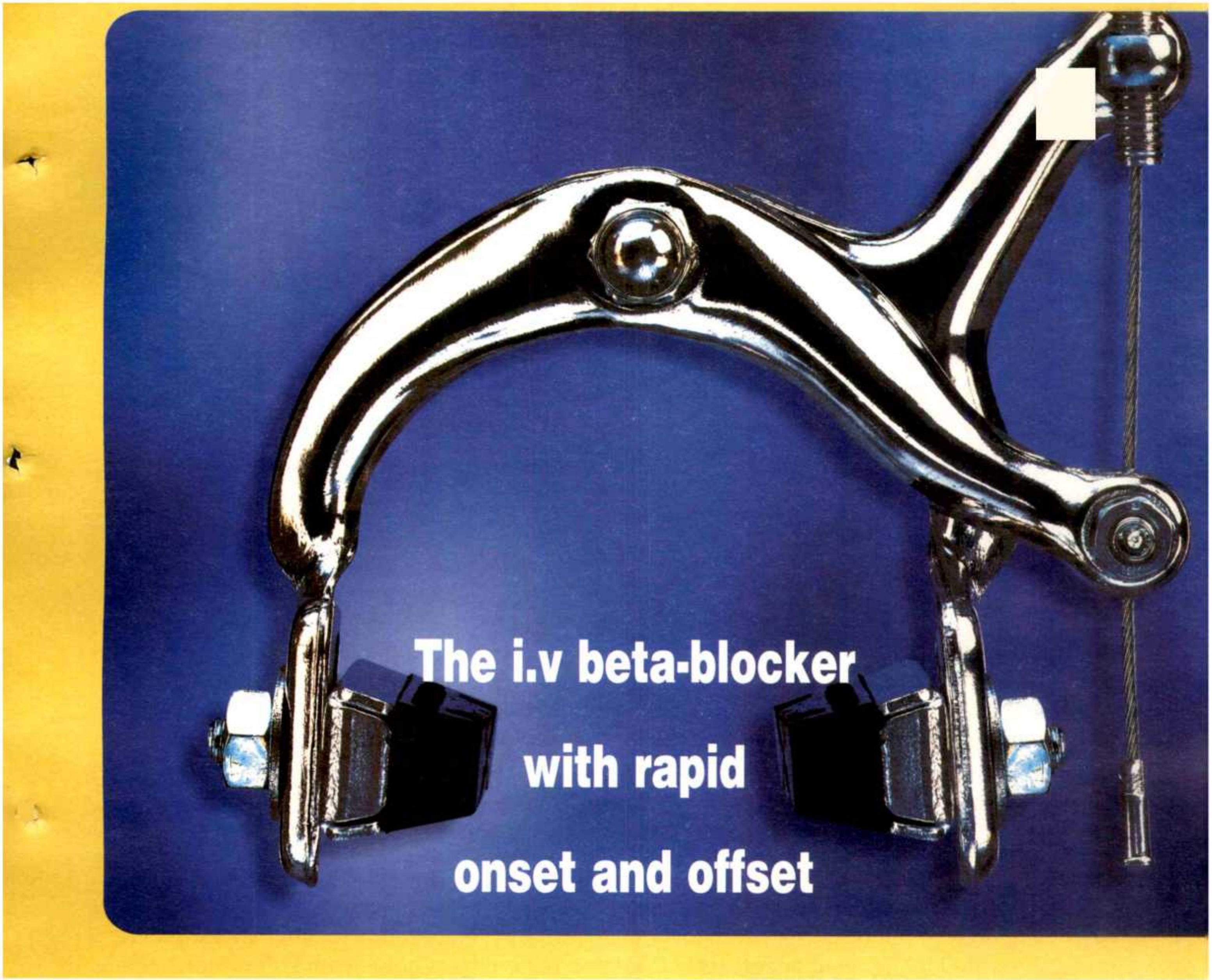

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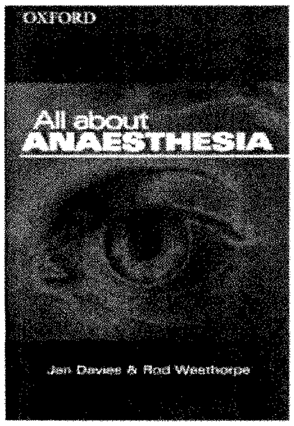

***Jan Davies**, Professor of Anaesthesia, Foothills Medical Centre, Calgary, Canada, and **Rod Westhorpe**, Deputy Director, Royal Children's Hospital, Melbourne, Australia*

Although anaesthesia has made possible many remarkable advances in medical treatment in the twentieth century, most patients know little about the procedure, and many of them are unduly apprehensive about its risks and consequences. This succinct, sympathetic and authoritative book aims to allay these anxieties. It covers all aspects of the procedure, including its history, variety, stages and possible complications.

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Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 2604472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Cross-piece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

4th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 8–11, 2001

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. New! Core Topics for your Personal Portfolio. Guest Speakers, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1, 2001. Meeting approved for CEPD.

For full information and to secure a place, please visit: www.anaesthesiaupdates.com or contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk

Annual Meeting of the International Society for Anaesthetic Pharmacology (ISAP) (formerly SIVA)

New Orleans, Louisiana, October 12, 2001

For further information contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: larshq@iars.org; Web address: www.isaponline.org

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.
Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

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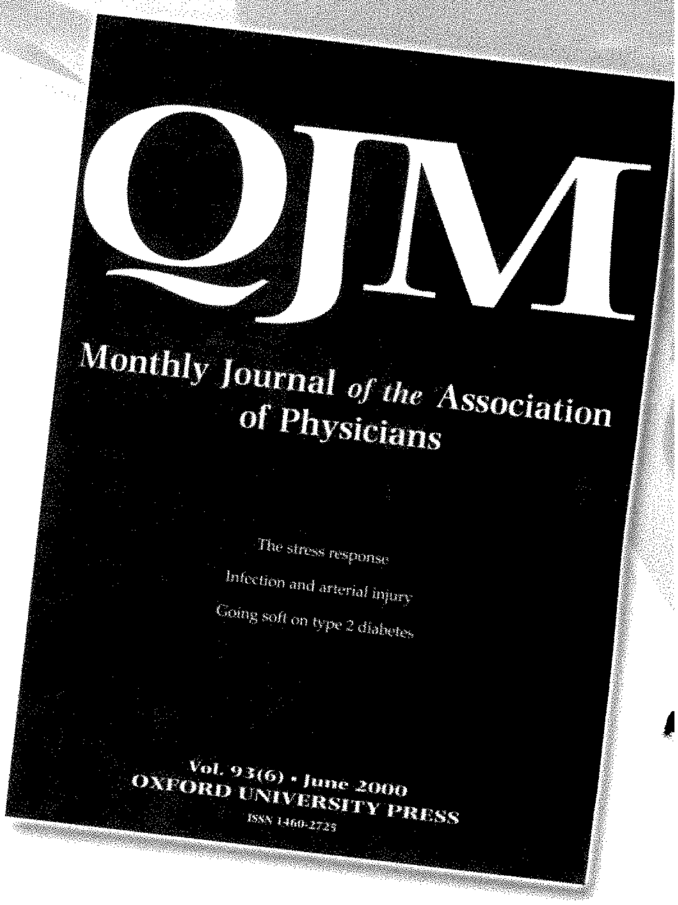

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Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

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International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

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First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Cross-piece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi

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Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

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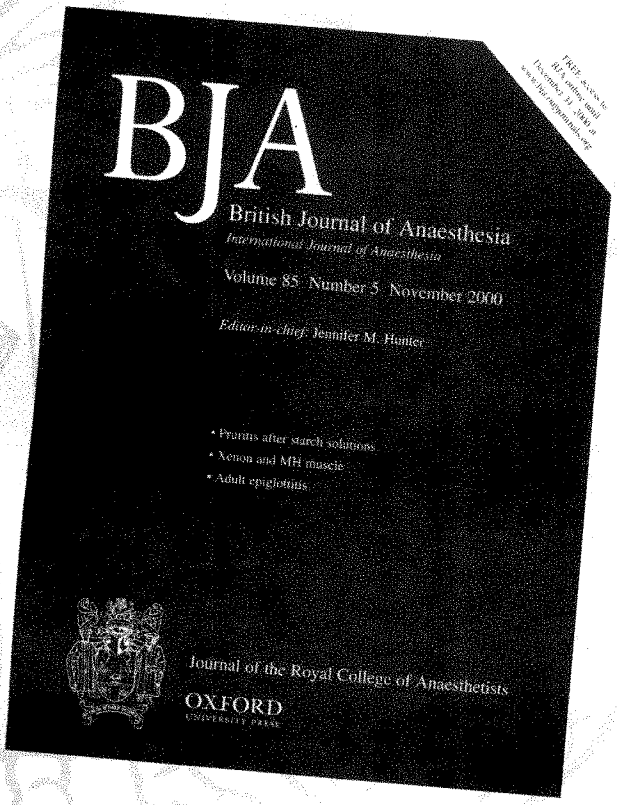

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Volume 85 Number 5 November 2000
Editor-in-chief: Jennifer M. Hunter
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ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib. VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded. *Elderly:* Exercise care when increasing the dose from 12.5 mg to 25 mg. *Hepatic insufficiency:* In mild hepatic insufficiency, do not exceed 12.5 mg once-daily. *Children:* Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs.
Third trimester of pregnancy and lactation. Inflammatory bowel dise
Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-exis
significantly impaired renal function, uncompensated heart fail
or cirrhosis. Use caution when initiating treatment in patients w
considerable dehydration. Rehydrate patients prior to star
therapy with rofecoxib. Consider the possibility of fluid retention
exercise caution when rofecoxib is used in patients with pre-exis
oedema, a history of heart failure, left ventricular dysfunctio
hypertension. Maintain appropriate supervision when treating
elderly or patients with renal, hepatic or cardiac dysfunction v
rofecoxib. In clinical studies, some osteoarthritis (OA) patients tre
with rofecoxib developed perforations, ulcers or bleeds (PU
Patients with a prior history of a PUB and patients *greater th*
years of age appeared to be at a higher risk for a PUB. At daily d
higher than 25 mg, the risks of gastro-intestinal symptoms, oede
or hypertension are increased. Elevations of ALT and/or AST
times the upper limit of normal) have been reported *in approxima*
1% of patients in clinical trials with rofecoxib. Any patient w
symptoms and/or signs suggesting liver dysfunction, or in whom
abnormal liver function test has occurred, should be evaluated
persistently abnormal liver function tests. If persistently abnormal l
function tests (three times the upper limit of normal) are detec
discontinue rofecoxib. Rofecoxib may mask fever. Use of rofeco
is not recommended in women attempting to conceive. *Interact*

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Landmark study supports superior GI safety profile compared with conventional NSAIDs

50% reduction in perforations, ulcers and bleeds (PUBs) compared with naproxen (95% CI 0.3-0.6; p=0.001)

*VIGOR – **V**IOXX **G**astro-intestinal **O**utcomes **R**esearch – a landmark study involving 8,076 rheumatoid arthritis patients monitored for GI events[1]. VIOXX is not licensed for rheumatoid arthritis. Patients were randomised to either VIOXX 50 mg once daily, or naproxen 500 mg twice daily for an average of nine months.

Rarely, patients may develop perforations, ulcers and bleeds with VIOXX, but the risk is lower in patients treated with VIOXX than in patients treated with conventional NSAIDs.

'VIOXX' IS LICENSED FOR OSTEOARTHRITIS ONLY, AT A DOSE OF 12.5 mg OR 25 mg ONCE DAILY

rmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated or changed in patients iving warfarin or similar agents, particularly in the first few days. *-inhibitors:* administration of 25 mg daily of rofecoxib with zepril, 10 mg to 40 mg daily for four weeks to patients with rtension was associated with a small attenuation of the ypertensive effect compared to the ACE inhibitor alone. This ld be considered in patients taking rofecoxib concomitantly with inhibitors. *Beta-blockers and diuretics:* concomitant use of IDS may reduce the antihypertensive efficacy of beta-blockers diuretics and the other effects of diuretics. *Aspirin:* at steady state, coxib 50 mg once-daily had no effect on the anti-platelet activity ow-dose (81 mg once-daily) aspirin. Avoid concomitant inistration of rofecoxib with higher doses of aspirin or other IDS. *Cyclosporin/tacrolimus:* monitor renal function when xib and either cyclosporin or tacrolimus is used in combination. *tions (pharmacokinetic): Lithium:* NSAIDS may increase na lithium concentrations. *Methotrexate:* consider adequate itoring for methotrexate-related toxicity when rofecoxib and otrexate are administered concomitantly. *CYP1A2 substrates:* cise care with concomitant administration of rofecoxib with drugs arily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, e and zileuton). *Midazolam:* a modest 30% reduction of the AUC idazolam was seen with rofecoxib 25 mg daily, most likely due creased first pass metabolism through induction of intestinal 3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a st induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25-mg dose when rofecoxib is used with potent inducers of hepatic metabolism. Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *Pregnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus. *Lactation:* contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common ($\geq 1/100$, $<1/10$); Uncommon ($\geq 1/1000$, $<1/100$); Rare ($\geq 1/10{,}000$, $<1/1000$); Very rare ($<1/10{,}000$) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity includi hepatic failure and jaundice.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspensi 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers:

Tablet 12.5 mg: PL 0025/0383; Tablet 25 mg: PL 0025/038 Oral Suspension 12.5 mg/5 ml: PL 0025/0385; Oral Suspensic 25 mg/5 ml: PL 0025/0386.

Marketing Authorisation holder: Merck Sharp & Dohme Limit Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** February 2001

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References:

1. Bombardier C, Laine L, Reicin A et al. Comparison of upp gastro-intestinal toxicity of rofecoxib and naproxen in patients wi rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528.

MSD

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9B

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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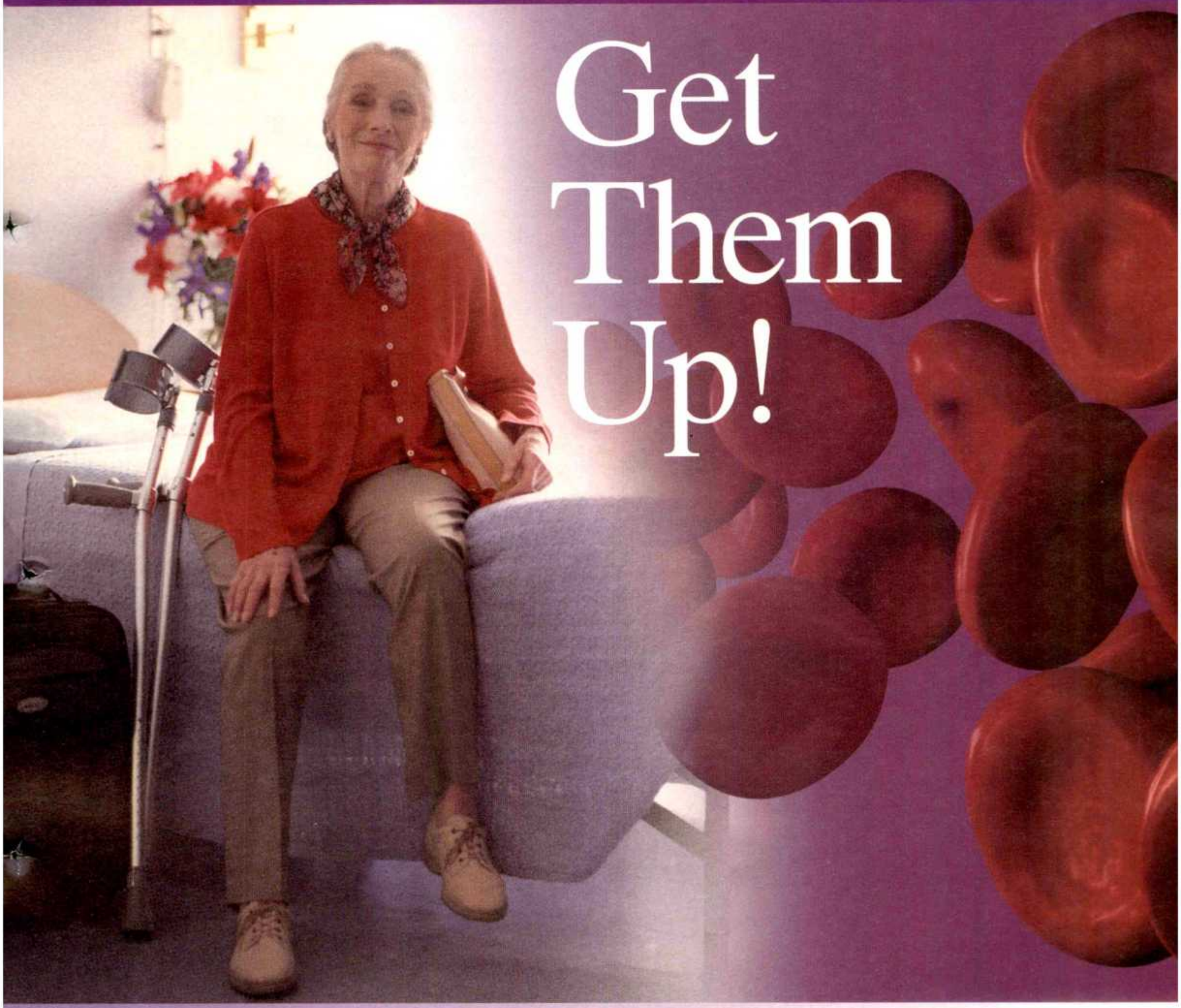

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Abbreviated version of the International summary of product characteristics Therapeutic indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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more rapid emergence and recovery[2]

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Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.
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BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 87, Number 1, July 2001

Editorial

Advances in pain

Developments in our understanding of the aetiology and management of acute and chronic pain are progressing at a pace and the time is right for a Postgraduate Educational Issue of the *British Journal of Anaesthesia* to consider this important area. The *British Journal of Anaesthesia* is very grateful to the many expert contributors to this issue which represents a comprehensive and authoritative review of several important areas of scientific and clinical interest.

The emphasis of this edition is clinical. However, the first two articles give an excellent overview of advances in our understanding of the basic sciences with respect to pain. Kidd and Urban[1] describe mechanisms of inflammatory pain and summarize the role of receptors, ion channels and neurotransmitters in the modulation of chemical, thermal and mechanical transduction. They describe how research in this field is driving the development of analgesics and anti-inflammatory drugs with novel modes of action. Neuropathic pain originates in a damaged or abnormal nervous system and differs in many respects to nociceptive pain and Bridges, Thompson and Rice review its aetiology.[2] They emphasize that a single mechanism is not likely to explain all syndromes of neuropathic pain and that improved understanding of this complex topic may allow mechanism- rather than disease-based approaches to therapy as suggested recently by Woolf and Mannion.[3] However, without the availability of new drugs acting at a variety of sites this is not, as yet, a practical proposition and Bridges and colleagues point towards future developments in this area.

For many years, bupivacaine has been the standard local anaesthetic for perioperative neural blockade. Concerns with respect to its safety, and our appreciation of the relative toxicities of stereoisomers, has led to the introduction of ropivacaine and levobupivacaine. Whiteside and Wildsmith[4] review the clinical efficacy of these new local anaesthetic agents in various clinical settings and compare their properties with bupivacaine. There is a world-wide drive to increase the number of surgical procedures performed on a day-case basis and adequate post-operative pain relief is essential if this is to succeed. Rawal reviews the techniques available for analgesia after day-case surgery and emphasizes the need for rapid return to 'street fitness' in these patients, the efficay of balanced analgesia utilizing local anaesthetic techniques and oral non-opioid analgesia and the role of post-discharge patient follow up.[5] He also considers more ambitious approaches, such as the use of spinal anaesthesia and patient-controlled regional analgesia systems.

Patient-controlled analgesia (PCA) and epidural analgesia have become the mainstay of post-operative pain relief in most countries and the literature with respect to their efficacy and safety is extensive. The nature of the data (e.g. poor study design) make interpretation difficult and time-consuming but our contributors have produced excellent reviews. Macintyre demonstrates that PCA can be very safe and effective but she emphasizes that prescriptions need to be adjusted to fit individual patients if maximum efficacy is to be achieved.[6] For many years, Wheatley has been a major advocate for the use of epidural analgesia after surgery and, with his colleagues Schug and Watson, considers the evidence for its efficacy and safety.[7] The scope of the review is extensive and includes consideration of factors such as choice of drug (e.g. opioid, local anaesthetic or mixture), site of epidural insertion, bolus *vs* infusion *vs* patient-controlled administration and the use of adjuvants. Safety is of major concern and the authors are able to give likely incidences of rare but serious side-effects, such as major neurological complications.

The Holy Grail of many workers investigating methods of optimal post-operative analgesia has been to demonstrate improved surgical outcome e.g. morbidity, mortality, hospital stay. Most have been disappointed. Kehlet has led the way in this field for several years and, with his colleague Holte, he reviews the relevant literature.[8] They conclude that better pain relief in itself is not likely to improve outcome, especially with respect to mobilization and hospital stay, unless it is part of a muti-disciplinary rehabilitation programme which maximizes the benefits of improved pain relief.

Unfortunately, evidence from pain clinics suggests that chronic pain may be an outcome of surgery for many patients. Macrae describes the common syndromes and gives some indication of their incidence.[9] He argues that this is a major problem and, until recently, a neglected topic. Pain may be relatively common after a number of procedures (e.g. breast surgery, thoracotomy, cholecystectomy,

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hernia repair) and he emphasizes the need for further research of good quality in order to elucidate the true incidence, risk factors and causes of this phenomenon. Phantom limb pain is a common example of chronic pain after surgery and, although this is described briefly by Macrae, the syndrome is comprehensively reviewed by Nikolajsen and Jensen;[11] workers who have made an enormous contribution to our understanding of this problem. They stress the importance of the differentiation between stump pain, phantom sensation and phantom pain and that a number of mechanisms are involved in the aetiology of this syndrome, including factors in the peripheral nervous system, spinal cord and brain. Evidence with respect to treatment and prevention is reviewed and they conclude that it may not be possible to prevent phantom pain with preemptive approaches.

There have been recent advances in our understanding of several chronic pain conditions and, in this issue, both complex regional pain syndrome (CRPS) and trigeminal neuralgia are reviewed. In a masterful review of the extensive and confusing literature on CRPS (formerly reflex sympathetic dystrophy), Harden considers important controversial factors such as epidemiology, diagnostic criteria and treatment.[10] He emphasizes that a multidisciplinary approach (i.e. doctors, physiotherapists, occupational therapists, psychologists) in the management of this devastating condition is essential and, although data from good quality clinical trials are lacking, patients often require the expert use of pharmacotherapy and blocks to support the multidisciplinary approach.

One of the most unpleasant conditions that can befall a patient is trigeminal neuralgia and this is reviewed by Nurmikko and Eldridge.[12] Again, diagnostic criteria can be confusing and several causes are likely to be responsible for the syndrome. The authors give expert guidance on diagnosis and show that the trigeminal nerve, rather than the central nervous system, is the likely site of pain generation. They also present clearly the published evidence for the short- and long-term efficacy of the numerous treatments for trigeminal neuralgia.

The controlled use of opioids for non-cancer chronic pain has been advocated by many and Collett reviews this controversial area.[13] She evaluates current practice and examines the evidence for and against this therapy. There are many published guidelines but most conform to a consensus view which is described in the article.

Finally, pain is a subjective, emotional complaint and, to manage it successfully, the practitioner must have an understanding of the psychological aspects. Eccleston reviews pain-related fear and depression and the phenomenon of coping and explains why extent of injury and disability are often poorly related to pain.[14] These factors play a central role in pain management programmes for patients with chronic pain and the efficacy of this approach is reviewed. The article is essential reading for all those involved in the management of acute and chronic pain.

We believe that this Postgraduate Educational Issue of the *British Journal of Anaesthesia* is an important addition to the literature on pain and pain management. We hope that it will be of use to specialists in this area but also inspire others to develop an interest in pain and even consider a career in this complex, challenging but rewarding area of clinical practice.

David J. Rowbotham
Department of Anaesthesia,
Intensive Care and Pain Management,
University of Leicester
Infirmary Road
Leicester LE1 5WW

References

1 Kidd BL, Urban LA. Mechanisms of inflammatory pain. *Br J Anaesth* 2001; **87**: 3–11
2 Bridges D, Thompson SWN, Rice ASC. Mechanisms of neuropathic pain. *Br J Anaesth* 2001; **87**: 12–26
3 Woolf CJ, Mannion RJ. Pain: Neuropathic pain: aetiology, symptoms, mechanisms and management. *Lancet* 1999; **353**: 1959–64
4 Whiteside JB, Wildsmith JAW. Developments in local anaesthetic drugs. *Br J Anaesth* 2001; **87**: 27–35
5 Rawal N. Analgesia for day case surgery. *Br J Anaesth* 2001; **87**: 73–87
6 Macintyre PE. Safety and efficacy of patient-controlled analgesia. *Br J Anaesth* 2001; **87**: 36–46
7 Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* 2001; **87**: 47–61
8 Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87**: 62–72
9 Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**: 88–98
10 Harden RN. Complex regional pain syndrome. *Br J Anaesth* 2001; **87**: 99–106
11 Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth* 2001; **87**: 107–16
12 Nurmikko TJ, Eldridge PR. Trigeminal neuralgia. *Br J Anaesth* 2001; **87**: 117–32
13 Collett B-J. Chronic opioid therapy for non-cancer pain. *Br J Anaesth* 2001; **87**: 133–43
14 Eccleston C. Role of psychology in pain management. *Br J Anaesth* 2001; **87**: 144–52

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Mechanisms of inflammatory pain

B. L. Kidd[1]* and L. A. Urban[2]

[1]Reader in Rheumatology, St Bart's and Royal London School of Medicine, Turner Street, London E1 2AD, UK. [2]Deputy Head, Novartis Institute for Medical Sciences, 5 Gower Place, London WC1E 6BN, UK

**Corresponding author*

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One of the cardinal features of inflammatory states is that normally innocuous stimuli produce pain. Since the publication of the Melzack–Wall gate control theory in 1965,[45] it has been widely appreciated that the nervous system exhibits a range of responses according to different conditions ('neural plasticity'). Subsequent research has characterized the mechanisms by which these changes occur and highlighted the importance of environmental factors on perception of pain.

This review focuses on key peripheral mechanisms that result in the hypersensitivity state that accompanies inflammation. Recent studies are described which characterize a series of receptors, ion channels and transmitters involved in inflammatory pain. The mechanisms by which inflammatory mediators interact with neurones to produce hypersensitivity are also explored.

The process of pain

In clinical settings it may be useful to identify several broad processes as being associated with pain: nociception, pain perception and a number of secondary consequences including suffering and pain behaviour.[38] Under this schema, nociception may be defined as the detection of noxious stimuli and the subsequent transmission of encoded information to the brain. In contrast, pain is essentially a perceptual process that arises in response to such activity (see Figure 1).

Symptoms and signs arising from normal tissues exposed to high intensity stimuli generally reflect the intensity, localization and timing of the initiating stimuli. In contrast, pain arising from inflamed or injured tissues may arise spontaneously in the absence of an external trigger. Alternatively, responses to noxious stimuli may be enhanced (hyperalgesia) or normally innocuous stimuli may produce pain (allodynia). These features are not specific and do not, in themselves, allow recognition of distinct pathophysiological mechanisms. The movement-related symptoms of osteoarthritis and the touch-evoked pain of herpetic neuralgia are both examples of mechanical allodynia although they clearly arise from different mechanisms. Given limitations with present terminology, the word hyperalgesia will be adopted throughout this review to describe the state of pain hypersensitivity that accompanies inflammation.

Nociception

Cutaneous and deep somatic tissues are innervated by primary afferent neurones that synapse with second-order neurones in the dorsal horn of the spinal cord. Primary afferent neurones have three functions with respect to their role in nociception: detection of noxious or damaging stimuli (transduction); passage of the resulting sensory input from peripheral terminals to the spinal cord (conduction); and synaptic transfer of this input to neurones within specific laminae of the dorsal horn (transmission). Sensory information arising from noxious stimuli is then relayed to supraspinal structures including the thalamus and the brainstem. Powerful internal controls are present at all levels, as exemplified by descending modulatory systems.

Transduction

The properties of receptors that detect either normal low-intensity stimuli or intense noxious stimuli differ in many important respects. Receptors for non-painful stimuli (such as light touch or movement) are characterized by specificity for a particular stimulus, a high degree of gain to amplify weak signals and rapid adaptation to increasing signal intensities.[19] In contrast, specificity is not so important after a noxious stimulus where the primary imperative is to

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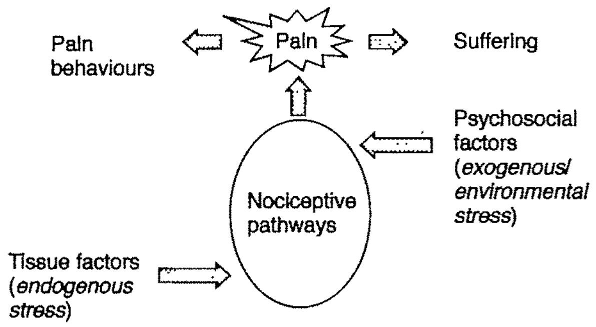
Pain behaviours
Pain
Suffering
Psychosocial factors (*exogenous/ environmental stress*)
Nociceptive pathways
Tissue factors (*endogenous stress*)

Fig 1 Processes of pain. Activity in nociceptive pathways leads to the experience of pain. Such activity can be stimulated or modified by both endogenous and exogenous stress. Endogenous stressors include damage and/or inflammation within both neuronal and non-neuronal tissues whereas exogenous stress may be produced by psychosocial factors. The resultant pain behaviours and suffering can be measured and provide useful parameters for clinical assessment.

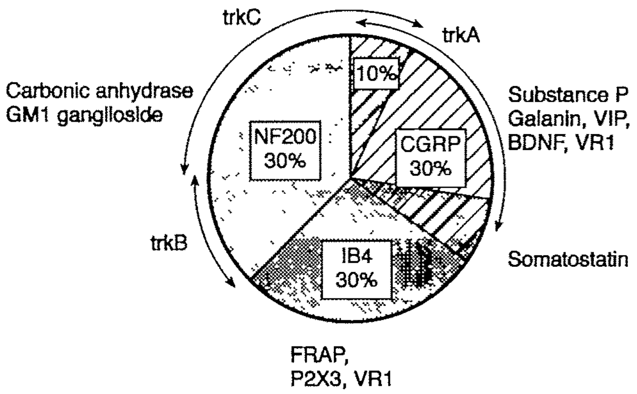

Fig 2 Pie chart summarizing the three main populations of DRG cells observed in rodents and their expression of neurotrophin receptors. Large diameter cells give rise to myelinated axons and have high levels of neurofilament (NF200). Small cells, with mainly unmyelinated axons, comprise the remaining two populations. One population of small cells constitutively synthesizes neuropeptides and responds to the growth factor, NGF, whereas the other expresses the lectin IB4 and responds to GDNF. Both small cell populations express the VR-1 receptor and are thought to be nociceptors (figure kindly provided by J. V. Priestley).

protect and remove the affected area as quickly as possible. Most high-threshold receptors therefore respond to a variety of thermal, chemical and mechanical stimuli and are defined as polymodal nociciceptors. A further and clinically relevant characteristic is that far from adapting to an ongoing stimulus, the threshold for activation of nociceptors may in fact fall such that relatively trivial stimuli now produce pain. This process of 'sensitization' will be discussed in later sections.

Conduction

Within adult dorsal root ganglia (DRG), large diameter cells have high levels of neurofilament and give rise to myelinated $A\beta$ fibres and a proportion of more thinly myelinated $A\delta$ fibres. Representing about 40% of lumbar DRG cells, they express trkB and trkC, which are high-affinity tyrosine kinase receptors for brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), respectively.[47] In contrast, small diameter cells give rise to mainly unmyelinated axons. They can be differentiated histochemically into two distinct populations including those cells which constitutively synthesize neuropeptides and those which bind the lectin IB4 (Fig. 2).

There is an extensive overlap (around 92%) between small cells expressing neuropeptides and the high-affinity receptor for nerve growth factor (NGF), trkA.[4] These cells, which are at least partially regulated by NGF, project to areas associated with nociceptive transmission and may be involved in neuromodulation and peripheral neurogenic inflammation.[63] The IB4 population of cells express trkA and respond to NGF in development, but trkA expression is down-regulated in the early postnatal period.[6] These cells express the receptor for tyrosine kinase, c-ret, and are regulated by glial cell line-derived neurotrophic factor (GDNF).[8] Although their exact function remains unclear, many of these cells express vanilloid receptor-1 (VR-1) and are thought to be nociceptors.

Neurophysiological studies confirm that, under normal conditions, rapidly conducting $A\beta$ fibres (with conduction velocities $>30\ \mathrm{m\ s^{-1}}$) are mainly concerned with non-noxious input from specialized encapsulated receptors. In contrast, most small diameter fibres, including $A\delta$ fibres (with conduction velocities of $2.5\text{–}30\ \mathrm{m\ s^{-1}}$) and C fibres (conduction velocities $<2.5\ \mathrm{m\ s^{-1}}$), have free nerve endings and respond to noxious stimuli (Fig. 3).[30] Whilst most C fibres show polymodal responses, some are exclusively chemosensitive under normal conditions and do not respond to mechanical and thermal stimuli. These silent or 'sleeping' nociceptors were first described in joints but were later found in other tissues.[60]

Transmission

In the first instance, spinal responses to non-tissue-damaging noxious stimuli are mediated by the excitatory amino acid, glutamate, acting on α-amino-3-hydroxy-5-methylisoxazole (AMPA) receptors. Importantly, repetitive stimulation or greater stimulus intensities, such as those associated with tissue damage, are associated with the functional expression of a second glutamate-responsive receptor, the *N*-methyl-D-aspartate (NMDA) receptor.[25] Activation of this receptor produces a sequence of events leading to increased excitability of dorsal horn neurones (Fig. 4).

Greater stimulus intensities are associated with the release of neuropeptides, including substance P, from central terminals of C fibres. Substance P, acting via

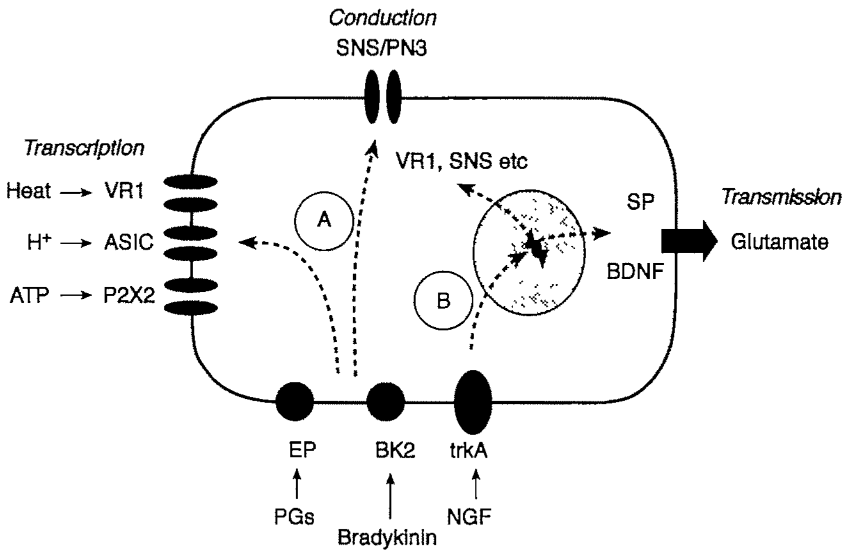

Fig 3 Influences on primary afferent neurones leading to 'peripheral sensitization'. Under normal circumstances, high-intensity stimuli are encoded by specialized membrane-bound receptors. Conduction of message to central terminals and transmission to spinal neurones is mediated by ion channels and excitatory amino acids, respectively. (A) During the early stages of inflammation, mediators such as prostaglandins (PGs) and bradykinin (BK) change the sensitivity of receptors and reduce activation threshold for conducting ion-channels. (B) Longer-term changes include transcriptional events mediated by cytokines and growth factors resulting in enhanced production of receptors, ion channels and central transmitters/modulators (modified from reference 74).

neurokinin (NK-1) receptors located on dorsal horn neurones, generates a greater post-synaptic response and enhances the activity of NMDA receptors.[66] This interaction takes place through the activation of protein kinase C, which phosphorylates the NMDA receptor, thereby changing its responsiveness to subsequent stimuli. Under normal circumstances, Mg^{2+} binding blocks the NMDA receptor but the alteration in Mg^{2+} binding kinetics allows release of Mg^{2+} from the receptor and permits glutamate-induced activation and subsequent depolarization of the cell membrane.[74]

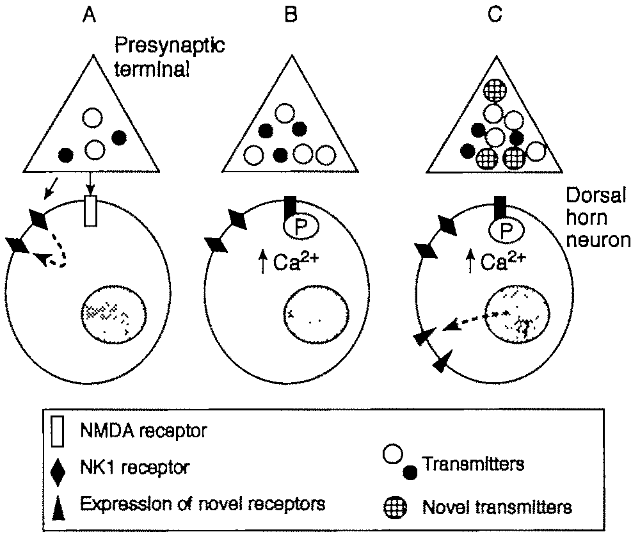

Fig 4 Development of 'central sensitization' in the spinal dorsal horn after inflammation of peripheral tissues. (A) Early phase with activation of C fibres: Glutamate (open spheres) and substance P (black spheres) are released from C fibres. Glutamate and substance P NK1 receptors are activated in dorsal horn neurones with the latter undergoing internalization and recirculation to the membrane. (B) Sensitization phase: Pre-synaptic up-regulation of neurotransmitter production together with ongoing activity in C fibres results in increased transmitter release with sustained influx of Ca^{2+} ions into dorsal horn neurones. Phosphorylation of the NMDA receptor by activated kinases allows the NMDA receptor to operate at resting membrane potential level and further enhances the accumulation of intracellular Ca^{2+}. (C) Established phase of chronic inflammatory pain. Synthesis of novel transmitters, growth factors and ion channels may lead to phenotypic changes within the nociceptive system (e.g. production of substance P in large fibres).

Receptors

The detailed biochemical and cellular mechanisms underlying the detection of painful stimuli are being revealed as more molecules are cloned and their function is elucidated. Recently, a series of ion-channel-linked receptors related to sensory transduction of noxious stimuli has been described. These include heat-activated vanilloid receptors and others sensitive to protons and products of purine metabolism.

Vanilloid receptors

Most nociceptors can be characterized by their sensitivity to capsaicin, the active ingredient in spicy 'hot' foods. One of the major advances in pain research over the past decade has been the isolation of a functional cDNA encoding the capsaicin receptor in sensory neurones.[16] VR-1 is a ligand-gated, non-selective cation channel. It belongs to a family of receptors that also includes the vanilloid receptor-like protein (VRL-1) and the stretch-inactivated channel (SIC). VR-1 is primarily distributed in small diameter afferent neurones although recently a more widespread expression in the central nervous system (CNS) has been described.[46]

In addition to being sensitive to capsaicin, VR-1 responds to moderate thermal stimuli (approximately 43°C), suggesting a heat-transduction role for this receptor. Interestingly, VRL-1 does not respond to capsaicin or moderate heat but is activated by high temperatures with a threshold of approximately 52°C.[17] Two recent studies[18 22] have demonstrated normal responses to acute noxious thermal stimuli in VR-1 knockout mice. However, hyperalgesic responses in a variety of inflammatory models were substantially attenuated or absent. Significantly, mechanical hyperalgesia was unaffected.

VR-1 responds to protons,[49] suggesting that its activity might be enhanced within the acidic environment of inflamed tissues. Other putative endogenous ligands include the cannabinoid receptor agonist anandamide[78] and the lipoxygenase product 12-(*S*)-hydroperoxy-eicosatetraenoic acid (12-(*S*)-HPETE).[33] Taken together, current evidence supports the conclusion that vanilloid receptors respond to multiple pain-producing stimuli, but whether VR-1 and related receptors play some form of integrative role following tissue injury remains unclear (for reviews see references 56 and 65).

Acid-sensing receptors

Recently, a new family of ion channels which are selectively activated by protons has been described.[69] These channels belong to the acid-sensing ion-channel (ASIC) group of receptors, which respond to low pH by producing a rapidly inactivating current in addition to a sustained sodium current.[68] They occur widely throughout the nervous system, with the ASIC-3 (DRASIC) subtype being most closely associated with dorsal root ganglion cells.[68] In addition to responding to acidic environments, it has been postulated that certain subtypes of ASIC receptors, together with stomatins, might also be involved in mechanosensitivity.[70]

Purinergic receptors

Adenosine and related phosphate derivatives (AMP, ADP and ATP) have been shown to produce pain in human subjects.[13] P2X purinoreceptors are ionotropic ligand-gated ion channels mediating fast synaptic transmission by extracellular ATP.[14] One receptor subtype, P2X3, is expressed selectively in small diameter neurones that label with the lectin IB4, suggesting that it plays a role in nociception. Responses to ATP are enhanced during inflammation in a number of experimental models; it has been suggested that sympathetic nerves, vascular endothelial cells or epithelial cells were the source of endogenous ATP in these models.[15]

Ion channels

Conduction with the nervous system is mediated in the first instance by voltage-gated ion channels. Although ion channels have a ubiquitous distribution, recent studies have identified a number of channels that appear to have a more selective role in nociception.

Sodium channels

Sodium channels can be classified into those that are sensitive to the puffer fish toxin tetrodotoxin (TTX-S) and those that are resistant (TTX-R). Whereas large diameter neurones express only TTX-S sodium channels, small diameter nociceptor neurones express both TTX-S and TTX-R channels.[29] Two sensory neurone-specific TTX-R sodium channels have been cloned, termed SNS/PN3 and SNS2/NaN, respectively.[1] The SNS/PN3 channel is closely associated with the nociceptor population within DRG[51] and the amounts of SNS/PN3 protein are increased during chronic inflammation.

Consistent with a role for SNS/PN3 in inflammatory pain states, prostaglandin E2 (PGE2), adenosine and serotonin all enhance channel sensitivity[27] and intrathecal administration of SNS/PN3 antisense oligonucleotides reverses inflammation-induced hyperalgesia.[55] Local anaesthetics, such as lignocaine, and anticonvulsants, including carbamazepine and phenytoin, block sodium channels but side effects within the CNS and elsewhere limit their widespread clinical application. By selectively affecting generation of action potentials in nociceptive neurones, blockade of TTX-R channels presents an attractive and highly specific therapeutic strategy for relieving both neuropathic and chronic inflammatory pain states.

Calcium channels

A range of voltage-gated calcium channels have been identified as being involved in transmitter release and prolonged excitatory states of the neuronal membrane.[67] It is noteworthy that the anticonvulsant gabapentin and related structures have high affinity and specificity for the $\alpha 2\delta$ subunit of these channels.[28] Gabapentin has found widespread acceptance in patients with diabetic and postherpetic neuralgia,[32] but appears to be less effective in individuals with inflammatory pain. Similarly, blocking calcium channels using ω-conotoxin, a toxin derived from snails of the genus *Conus*, produces analgesia[76] but the effect does not allow differentiation between the various channels and has a limited therapeutic window. Potentially, selective blockade of the pre-synaptic N-type channel, which controls transmitter release at the dorsal horn, provides a useful target for broad-spectrum analgesics.

Plasticity

Plasticity may be regarded as the property of the nervous system that enables it to modify its function according to different conditions.[21] It is pivotal to the development of the hypersensitivity state that underlies inflammatory pain. Ongoing studies are revealing how pain hypersensitivity is the consequence of early post-translational changes, including phosphorylation of membrane-bound proteins, as well as later transcription-dependent changes in effector genes at multiple levels along the nociceptive pathway.

Peripheral sensitization

Tissue injury results in the release of inflammatory mediators from damaged cells including ions (K^+, H^+), bradykinin, histamine, 5-hydroxytryptamine (5-HT), ATP and nitric oxide. Activation of the arachidonic acid pathway leads to the production of prostanoids and leukotrienes. Recruited immune cells release further mediators including cytokines and growth factors. Some of these mediators activate peripheral nociceptors directly and lead to spontaneous pain, whereas others act indirectly via inflammatory cells to stimulate the release of additional pain-inducing (algogenic) agents. Importantly, inflammatory mediators also act to modify the response properties of primary afferent neurones to subsequent stimuli (peripheral sensitization). This may arise as a result of changes to the sensitivity of receptor molecules themselves, or via modulation of voltage-gated ion channels.

Bradykinin

Bradykinin is released on tissue injury and makes an important early contribution to the inflammatory cascade. When given experimentally to human subjects, it produces pain, inflammation and hyperalgesia.[44] Bradykinin and kallidin together with their degradation products des-Arg^9 bradykinin and des-Arg^9-kallidin have complex effects on primary afferent neurones, including both activation and sensitization by direct and indirect pathways (for a review see reference 26).

Bradykinin B2 receptors, which bind bradykinin and kallidin, are constituitively and abundantly expressed on both neurones and non-neuronal cells. Consistent with these findings, the selective and high affinity B2 receptor antagonist, Bradyzide, blocks inflammatory hyperalgesia in animal models.[12] In contrast to bradykinin, des-Arg^9 bradykin selectively activates B1 receptors. Interestingly, B1 receptor agonists produce pain only during inflammation, suggesting that enhanced expression of the B1 receptor or sensitization of the receptor is required.[26]

Cytokines

Cytokines play an important role in the initiation and maintenance of inflammatory diseases as mediators of cell–cell interactions. In addition to their enhancing and inhibitory effects on immune and inflammatory cells, cytokines exert considerable influence over sensory neurones. Similar to other mediators, cytokines may act directly on nociceptors or, more commonly, indirectly, stimulating the release of agents such as prostaglandins. During acute phases, cytokines appear to induce sensitization via receptor-associated kinases and phosphorylation of ion channels whereas in chronic inflammation transcriptional up-regulation of receptors and secondary signalling become more important.[52]

Most studies to date have focused on the pro-inflammatory cytokines including tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), IL-6 and the chemokine IL-8. Intradermal injections of these agents generally produce both mechanical and thermal hyperalgesia. Antibodies against TNFα reduce hyperalgesia in inflammatory models[75] and the use of novel anti-TNF therapies in rheumatoid arthritis is accompanied by substantial reductions in pain scores.[42] More modest reductions have been observed after anti-IL-1 therapy.[11] IL-6 knockout mice shown reduced mechanical and thermal hyperalgesia in response to inflammatory stimuli[77] or after chronic nerve constriction.[48]

Prostaglandins

Prostaglandins are important mediators of inflammation, fever and pain. They are synthesized by the constitutive enzyme, cyclo-oxygenase-1 (COX-1), and its isoform enzyme COX-2, which is induced in peripheral tissues by cytokines, growth factors and other inflammatory stimuli.[5] Although in some situations prostaglandins contribute to pain by directly activating nociceptors, they are generally considered to be sensitizing agents. Prostaglandins increase levels of cyclic AMP and may enhance nociceptor sensitization by reducing the activation threshold for TTX-R sodium channels via a protein kinase A pathway.[27] They sensitize primary afferent neurones to bradykinin and other mediators[50] and are likely to be involved at multiple sites along the nociceptive pathway.[59]

COX-1 and COX-2 have been identified in the brain and spinal cord of humans and rats and both appear to be constitutively expressed in these tissues.[71] Recent studies using selective COX knockouts have suggested that these enzymes might subserve different mechanistic pathways and are possibly gender specific.[5] Whereas COX-1-deficient mice show reduced nociceptive activity to a variety of noxious stimuli, less marked changes are observed in COX-2-deficient mice. Rather surprisingly, nociceptive activity is reduced only in models of slowly developing diffuse pain in female, but not male, COX-2-deficent mice. Furthermore, up-regulation of COX-1 has been observed in spinal tissues of COX-2-deficient mice whereas compensatory up-regulation of COX-2 has not been observed in COX-1-deficient animals.[5]

Growth factors

Neurotrophic growth factors, including NGF, make significant and long-lasting contributions to the changes of neurone sensitivity observed during inflammation. NGF mRNA and/or protein has been identified in various cell types including fibroblasts, keratinocytes, Schwann cells and a range of immune cells. A large number of inflammatory mediators act to increase NGF production, particularly IL-1β and TNFα.[75] Consistent with this, increased levels of NGF have been reported in animal models of inflammation and in human disorders including arthritis, cystitis and asthma.[39]

The importance of NGF in mediating inflammation-induced hyperalgesia has been highlighted by a number of studies showing very significant reductions in enhanced responses using a variety of anti-NGF strategies, including the use of novel sequestration antibodies (reviewed in reference 39). In human subjects, NGF produces cutaneous hyperalgesia at the injection site and widespread deep pain which persists for several days. It is probable these sensitizing effects are at least partially mediated by direct effects on nociceptors themselves and partially via mediators released by NGF-activated mast and other inflammatory cells. A role for sympathetic neurones has also been reported.

During the acute stages of an inflammatory response, neuronal trkA activation leads to tyrosine phosphorylation of intracellular targets including ion channels. Over the longer term, NGF exerts a more global influence by regulating the expression of the neuropeptides, substance P and calcium gene-related peptide (CGRP), as well as receptors including VR-1 and bradykinin B2, and ion channels such as SNS (reviewed in reference 35).

In addition to their classic trophic actions, neurotrophins can be synthesized by neurones and influence synaptic transmission. In particular, BDNF is synthesized by small DRG neurones, packaged in dense-cored vesicles, and transported within axons into terminals in the dorsal horn of the spinal cord.[47] BDNF has potent effects on spinal cord neurones and has been implicated in the central sensitization associated with inflammation.[43] Production of BDNF is increased by exogenous NGF[47] and by inflammation[20] and the increase in BDNF associated with inflammation can be reduced by treatment with antibodies to NGF.[20]

Neurogenic factors

The nervous system acts in concert with the immune and endocrine systems to constitute an interactive, communicative network. Neuropeptides such as substance P and CGRP are available for release from distal as well as central terminals of small diameter peptidergic neurones. They have a broad spectrum of effects within peripheral tissues and make a significant contribution to the so-called 'wheal and flare response' that follows cutaneous injury. In these circumstances, substance P is believed to act primarily on post-capillary venules to produce plasma extravasation, whereas CGRP acts on arterioles to produce vasodilation. A synergistic interaction between these peptides has been observed.[10]

It is probable that neuropeptides released from peripheral terminals make largely indirect contributions to nociceptor activity during inflammation. Although a detailed description of the pro-inflammatory effects of neuropeptides is beyond the scope of this review, most research to date has centred on substance P and related tachykinins (for a review see reference [40]). Substance P degranulates mast cells to produce histamine release, induces release of PGE2 and collagenase from synoviocytes and may stimulate the release of cytokines from macrophages, although this remains controversial.[37] Substance P has also been shown to have chemotactic properties with respect to T cells, monocytes, neutrophils and eosinophils.[31]

Inhibition of peripheral sensitization

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) act to inhibit COX enzymes and reduce the formation of prostaglandins. Whilst the non-selective inhibition of COX produces a significant antihyperalgesic effect and emphasizes the importance of prostaglandins in inflammatory hyperalgesia, clinical use is limited by serious gastrointestinal side effects (for a review see reference 53). The recent introduction of selective COX-2 inhibitors provides a potential means to reduce these effects. The analgesic efficacy of selective COX-2 inhibitors in rheumatoid arthritis appears similar to that of non-selective inhibitors,[62] although long-term studies are awaited.

To circumvent problems associated with COX, the actions of prostaglandins can be substantially reduced by selective receptor blockade. The most promising approach uses antagonists of the EP receptor subfamily, which are present on sensory neurones and are activated by PGE2. IP receptors may also contribute to the development of inflammatory hyperagesia, once activated by the inflammatory prostanoid PGI2. There is extensive experimental evidence for the pro-inflammatory effects of both PGE2 and PGI2 in the joint[34,61] and selective blockade of EP/IP receptors provides an effective antihyperalgesic strategy in animal models.[9]

A further alternative is offered by nitric oxide-releasing derivatives of NSAIDs.[24] Development of so-called nitroaspirin and various combination of NSAIDs with nitric oxide allows greater anti-nociceptive and anti-inflammatory effects in inflammatory models of pain compared with the parent NSAID without damage in the gastrointestinal tract.[2]

Opiates

Opiates are produced by immune cells, and opioid receptors are present in peripheral tissues.[64] Expression of μ, δ and κ receptors increases in primary afferent neurones during inflammation and selective agonists block spontaneous firing of fibres which innervate inflamed skin.[3] Opioid agonists developed for peripheral use (e.g. loperamide) show antinociceptive activity in inflammatory conditions such as experimental arthritis.[23] Potentially, peripherally acting opioid compounds may provide pain relief in inflammatory conditions by systemic or topical application.

Cannabinoids
A novel approach to inhibiting peripheral sensitization is provided by cannabinoids. Topical application of cannabinoid receptor agonists blocks nociception in inflammatory models of pain.[54] Consistent with this finding, the natural endogenous ligand of cannabinoid receptors, anandamide, when given systemically, exerts analgesia. There are two types of cannabinoid receptor, CB1 and CB2. The former is expressed on central and peripheral neurones as well as on non-neuronal cells, whereas the latter is of non-neuronal origin and is present on immune cells. Activation of the CB1 receptor is negatively coupled to adenylate cyclase and blocks excitability and activation of primary afferents.[58] Activation of the CB2 receptor may produce antinociceptive effects via inhibition of immune cell functions (for a review see reference 57).

In addition to central activity in pain pathways,[36] the strong peripheral presence of CB1 receptors in primary afferent neurones offers an alternative site for analgesic intervention. Although there is no doubt about the central antinociceptive effects of cannabinoids on their own and in co-operation with the opioid system,[57] the preferred route is the development of peripherally acting CB1 receptor antagonists, thereby prohibiting central side effects.

Central sensitization

Whilst pain hypersensitivity after an inflammatory stimulus is contingent to a large degree on peripheral sensitization, other mechanisms are also involved. Sustained or repetitive activation of primary afferent fibres produces substantial changes to the function and activity of central neurogenic pathways. In addition to glutamate, which dominates communication between the periphery and the spinal cord, neuropeptides such as substance P and neurotrophic factors such as BDNF are released from central terminals of primary afferents during inflammatory conditions. They serve to act as co-transmitters and induce long-lasting changes in spinal excitability known collectively as 'central sensitization' (Fig. 4).[73]

Increased release of peptide transmitters from primary afferent fibres activates second messenger systems and results in increased influx of Ca^{2+} ions and phosphorylation of proteins. During prolonged inflammation, activation of kinases produces transcriptional changes (for review see reference 74). The net result is that the responsiveness of dorsal horn cells, both to existing inputs and to previously sub-threshold inputs, is increased, producing: (i) exaggerated responses to normal stimuli; (ii) expansion of receptive field size; and (iii) reduction in the threshold for activation by novel inputs (e.g. from mechanoceptive A fibres).

The most plausible theory for central sensitization suggests that the NMDA receptor occupies a central position in this phenomenon. NMDA receptor antagonists are antinociceptive, but the therapeutic applicability of present antagonists is limited by the ubiquitous expression of the receptor. A number of endogenous mediators, including prostaglandins, nitric oxide, opioids and adrenergic agonists, also influence the excitability of spinal neurones. Whereas prostaglandins and nitric oxide appear to facilitate spinal excitability, $\alpha 2$ adrenergic and opioid receptor agonists produce analgesia by presynaptic inhibition of C-fibre neurotransmitter release and post-synaptic hyperpolarization of second-order neurones.[8] Co-administration of intrathecal morphine and selected $\alpha 2$ agonists or NSAIDs results in substantial analgesic synergy[41] and highlights a role for combination therapy in clinical settings.

Conclusions

The complex mechanisms underlying the modulation of mechanical, thermal and chemical transduction have started to emerge through the characterization of receptors, ion channels and neurotransmitter/modulator proteins. Changes in the sensitivity of nociceptive neurones underlie development of the tissue hypersensitivity associated with inflammation.

Recognition of the necessity for new strategies for the management of pain has led to the development of innovative drugs with favourable side-effect profiles. The introduction of ion channel blockers and selective inhibitors of COX-2 provides two obvious examples. Looking ahead, the characterization of specific pathophysiological changes underlying particular inflammatory diseases is set to produce a qualitative change in pain management and signals, for the first time, the possibility of diagnosis-based analgesic medication.

References

1 Akopian AN, Sivilotti L, Wood JN. A terodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature* 1996; **379**: 257–62

2 Al-Swayeh OA, Clifford RH, del Soldato P, Moore PK. Comparison of the anti-inflammatory and anti-nociceptive activity of nitroaspirin and aspirin. *Br J Pharmacolol*, 2000; **129**: 343–50

3 Andreev N, Urban L, Dray A. Opioids suppress spontaneous activity of polymodal nociceptors in rat paw skin induced by ultraviolet irradiation. *Neuroscience* 1994; **58**: 793–8

4 Averill S, McMahon SB, Clary DO, Reichart LF, Priestley JV. Immunocytochemical localization of trkA receptors in chemically identified subgroups of adult rat sensory neurons. *Eur J Neurosci* 1995; **7**: 1484–94

5 Ballou LR, Botting RM, Goorha S, Zhang J, Vane JR. Nociception in cyclooxygenase isozyme-deficient mice. *Proc Natl Acad Sci USA* 2000; **97**: 10272–6

6 Bennett DLH, Averill S, Clary DO, Priestley JV, McMahon SB. Postnatal changes in the expression of the trkA high-affinity NGF

receptor in primary sensory neurons. *Eur J Neurosci* 1996; **8**: 2204–8

7 Bennett DLH, Michael GJ, Ramachandran JB, *et al.* A distinct subgroup of small DRG cells express GDNF receptor components and GDNF is protective for these neurones after nerve injury. *J Neurosci* 1998; **18**: 3059–72

8 Besson JM. The neurobiology of pain. *Lancet* 1999; **353**: 1610–15

9 Bley KR, Hunter JC, Eglen RM, Smith JAM. The role of IP prostanoid receptors in inflammatory pain. *Trends Pharmacol Sci* 1998; **19**: 141–7

10 Brain SD, Williams TJ. Substance P regulates the vasodilator activity of CGRP. *Nature* 1988; **335**: 73–5

11 Bresnihan B, Alvo-Gracia JM, Cobby M, *et al.* Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; **41**: 2196–204

12 Burgess GM, Perkins MN, Rang HP, *et al.* Bradyzide, a potent non-peptide B2 bradykinin receptor antagonist with long-lasting oral activity in animal models of inflammatory hyperalgesia. *Br J Pharmacokol* 2000; **129**: 77–86

13 Burnstock G. A unifying purinergic hypothesis for the initiation of pain. *Lancet* 1996; **347**: 1604–5

14 Burnstock G, Wood JN. Purinergic receptors: their role in nociception and primary afferent neurotransmission. *Curr Opin Neurobiol* 1996; **6**: 526–32

15 Burnstock G, McMahon SB, Humphrey PPA, Hamilton SG. ATP (P2X) receptors and pain. In: Devor M, Rowbotham MC, Wiesenfeld-Hallin Z, eds. *Proceedings of the Ninth World Congress on Pain*. Seattle: IASP Press, 2000; 63–76

16 Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat activated ion channel in the pain pathway. *Nature* 1997; **389**: 816–24

17 Caterina MJ, Rosen TA, Tominaga MA, Brake AJ, Julius D. A capsaicin receptor homologue with a high threshold for noxious heat. *Nature* 1999; **398**: 436–41

18 Caterina MJ, Leffler A, Malberg AB, *et al.* Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 2000; **288**: 306–13

19 Cesare P, McNaughton P. Peripheral pain mechanisms. *Curr Opin Neurobiol* 1997; **7**: 493–9

20 Cho HJ, Kim SY, Park MJ, Kim DS, Kim JK, Chu MY. Expression of mRNA for brain derived neurotrophic factor in the dorsal root ganglion following peripheral inflammation. *Brain Res* 1997; **749**: 358–62

21 Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–85

22 Davis JB, Gray J, Gunthorpe MJ, *et al.* Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* 2000; **495**: 183–7

23 DeHaven-Hudkins DL, Burgos LC, Cassel JA, *et al.* Loperamide (ADL 2-1294), an opioid antihyperalgesic agent with peripheral selectivity. *J Pharmacol Exp Ther* 1999; **289**: 494–502

24 Del Soldato P, Sorrentino R, Pinto A. NO-aspirins: a class of new anti-inflammatory and antithrombotic agents. *Trends Pharmacol Sci* 1999; **20**: 319–23

25 Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent dependent potentiation of deep rat dorsal horn nociceptive neurones following C-fibre stimulation. *Neuropharmacology* 1987; **26**: 1235–8

26 Dray A, Perkins M. Bradykinin and inflammatory pain. *Trends Pharmacol Sci* 1993; **16**: 99–104

27 England S, Bevan SJ, Docherty RJ. Prostaglandin E2 modulates the tetrodotoxin-resistant sodium current in neonatal rat dorsal root ganglion neurones via the cyclic AMP–protein kinase A cascade. *J Physiol* 1996; **495**: 429–40

28 Gee NS, Brown JP, Dissanayake VUK, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the α2d subunit of a calcium channel. *J Biol Chem* 1996; **271**: 5768–76

29 Gold MS, Reichling DB, Shuster MJ, Levine JD. Hyperalgesic agents increase a tetrodotoxin-resistant Na$^+$ current in nociceptors. *Proc Natl Acad Sci USA* 1996; **93**: 1108–12

30 Grigg P, Schaible H, Schmidt RF. Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. *J Neurophysiol* 1986; **55**: 635–43

31 Hood V, Cruwys SC, Urban L, Kidd BL. Differential role of neurokinin receptors in human lymphocyte and monocyte chemotaxis. *Regul Peptides* 2000; **96**: 17–21

32 Hunter JC, Gogas KR, Hedley LR, *et al.* The effect of novel anti-epileptic drugs in rat experimental models of acute and chronic pain. *Eur J Pharmacol* 1997; **324**: 153–60

33 Hwang SW, Cho H, Hwang SW, *et al.* Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. *Proc Natl Acad Sci USA* 2000; **97**: 6155–60

34 Khasar SG, Ho T, Green PG, Levine JD. Comparison of prostaglandin E1- and prostaglandin E2-induced hyperalgesia in the rat. *Neuroscience* 1994; **62**: 345–50

35 Levine JD, Reichling DB. Peripheral mechanisms of inflammatory pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*. London: Churchill Livingstone, 1999; 59–84

36 Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *J Pharmacol Exp Ther* 1991; **21**: 311S–319S

37 Lieb K, Fieich BL, Busse-Grawitz M, Hull M, Berger M, Bauer J. Effects of substance P and selected other peptides on the synthesis of interleukin 1β and interleukin-6 in human monocytes: a re-examination. *J Neuroimmunol* 1996; **67**: 77–81

38 Loeser JD, Melzack R. Pain: an overview. *Lancet* 1999; **353**: 1607–9

39 McMahon SB, Bennett DL. Trophic factors and pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*. London: Churchill Livingstone, 1999; 105–28

40 Maggi CA. The effects of tachykinins on inflammatory and immune cells. *Regul Peptides* 1997; **70**: 75–90

41 Malmberg AB, Yaksh TL. Antinociceptove actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *J Pharmacol Exp Ther* 1992; **263**: 136–46

42 Mani RN, Breedveld FC, Kalden JR, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; **41**: 1552–63

43 Mannion RJ, Costigan M, Decosterd I, *et al.* Neurotrophins: peripherally and centrally acting modulators of tactile stimulus-induced inflammatory pain hypersensitivity. *Proc Natl Acad Sci USA* 1999; **96**: 9385–90

44 Meller ST, Gebhart GF. A critical review of the afferent pathways and the potential chemical mediators involved in cardiac pain. *Neuroscience* 1992; **48**: 501–24

45 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–9

46 Mezey E, Toth EZ, Cortright DN, *et al.* Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human. *Proc Natl Acad Sci USA* 2000; **97**: 3655–60

47 Michael GJ, Averill S, Nitkunan A, *et al.* Nerve growth factor treatment increases brain-derived neurotrophic factor selectively in trkA-expressing dorsal root ganglion cells and in their central terminations within the spinal cord. *J Neurosci* 1997; **17**: 8476–90

48 Murphy PG, Ramer MS, Borthwick L, Gauldie J, Richardson PM, Bisby MA. Endogenous interleukin-6 contributes to hypersensitivity to cutaneous stimuli and changes in neuropeptides associated with chronic nerve constriction in mice. *Eur J Neurosci* 1999; **11**: 2243–53

49 Nagy I, Rang HP. Similarities and differences between the responses of rat sensory neurons to noxious heat and capsaicin. *J Neurosci* 1999; **19**: 10647–55

50 Neugebauer V, Schaible H-G, Schmidt RF. Sensitization of articular afferents to mechanical stimuli by bradykinin. *Pflugers Arch* 1989; **415**: 330–35

51 Novakovic SD, Tzoumaka E, McGivern JG, *et al.* Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J Neurosci* 1998; **18**: 2174–87

52 Opree A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-α, IL-1β and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. *J Neurosci* 2000; **20**: 6289–93

53 Payne R. Limitations of NSAIDs for pain management: toxicity or lack of efficacy? *J Pain* 2000; **1**: 14–18

54 Piomelli D, Giuffrida A, Calignano A, Rodriguez de Fonseca F. The endocannabinoid system as a target for therapeutic drugs. *Trends Pharmacol Sci* 2000; **21**: 218–24

55 Porreca F, Porreca F, Lai J, *et al.* A comparison of the potential role of the tetrodotoxin-insensitive sodium channels, PN3/SNS and NaN/SNS2, in rat models of chronic pain. *Proc Natl Acad Sci USA* 1999; **96**: 7640–4

56 Reichling DB, Levine JD. In hot pursuit of the elusive heat transducers. *Neuron* 2000; **26**: 555–8

57 Richardson JD. Cannabinoids modulate pain by mechanisms of action. *J Pain* 2000; **1**: 2–14

58 Richardson J, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 1998; **75**: 111–19

59 Rueff A, Dray A. Sensitization of peripheral afferent fibres in the *in vitro* neonatal rat spinal cord by bradykinin and prostaglandins. *Neuroscience*, 1993; **54**: 527–35

60 Schaible H-G, Grubb BD. Afferent and spinal mechanisms of joint pain. *Pain* 1993; **55**: 5–54.7

61 Schepelmann K, Messlinger K, Schaible H-G, Schmidt RF. Inflammatory mediators and nociception in the joint: excitation and sensitization of slowly conducting afferent fibres of cat's knee by prostaglandin I2. *Neuroscience*, 1992; **50**: 237–47

62 Schnitzer T, Truitt K, Fleischmann R, *et al.* The safety profile, tolerability and effective dose range of celecoxib in the treatment of rheumatoid arthritis. *Clin Ther* 1999; **21**: 1688–702

63 Snider WD, McMahon SB. Tackling pain at the source: new ideas about nociceptors. *Neuron* 1998; **20**: 629–32

64 Stein C. Peripheral mechanisms of opioid analgesia. *Anesth Analg* 1993; **76**: 182–91

65 Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51**: 159–211

66 Thompson SWN, Dray A, Urban L. Injury-induced plasticity of spinal reflex activity: NK1 neurokinin receptor activation and enhanced A- and C-fiber mediated responses in the rat spinal cord *in vitro*. *J Neurosci* 1994; **14**: 3672–87

67 Veradi G, Mori Y, Mikala G, Schwartz A. Molecular determinants of Ca^{2+} channel function and drug action. *Trends Pharmacol Sci* 1995; **16**: 43–9

68 Waldmann R, Bassilana F, de Weil J, Champigny G, Heurteaux C, Lazdunski M. Molecular cloning of a non-inactivating proton-gated Na$^+$ channel specific for sensory neurons. *J Biol Chem* 1997; **272**: 20975–8

69 Waldmann R, Champigny G, Bassilana F, Heurteaux C, Lazdunski M. A proton-gated cation channel involved in acid-sensing. *Nature* 1997; **386**: 173–7

70 Waldmann R, Lazdunski, M. H($^+$)-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels. *Curr Opin Neurobiol* 1998; **8**: 418–24

71 Willingale HL, Gardiner NJ, McLymont N, Giblett S, Grubb BD. Prostanoids synthesized by cyclo-oxygenase isoforms in rat spinal cord and their contribution to the development of neuronal hyperexcitability. *Br J Pharmacolol* 1997; **122**: 1593–604

72 Wood JN, Docherty RJ. Chemical activation of sensory neurons. *Annu Rev Physiol* 1997; **59**: 457–82

73 Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983; **306**: 686–8

74 Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci USA* 1999; **96**: 7723–30

75 Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumor necrosis factor α. *Br J Pharmacolol* 1997; **121**: 417–24

76 Xiao W-H, Bennett GJ. Inhibition of neuropathic pain by N-type calcium channel blockade with omega conopeptides applied to the site of nerve injury. *Soc Neurosci Abstr* 1994; **20**: 559

77 Xu X, Hao J, Andell-Jonsson S, Poli V, Bartfai T, Wiesenfeld-Hallin Z. Nociceptive responses in interleukin-6-deficient mice to peripheral inflammation and peripheral nerve section. *Cytokine* 1997; **9**: 1028–33

78 Zygmunt PM, Petersson J, Andersson DA, *et al.* Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 1999; **400**: 452–7

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Mechanisms of neuropathic pain

D. Bridges[1] [2], S. W. N. Thompson[3] and A. S. C. Rice[1]*

[1]Pain Research, Department of Anaesthetics, Imperial College School of Medicine, Chelsea and Westminster Hospital Campus, London W2 1NY, UK. [2]Novartis Institute for Medical Sciences, 5 Gower Place, London, WC1, UK. [3]Centre for Neuroscience Research, Kings College London, Guys Hospital, London, UK

**Corresponding author: Department of Anaesthetics, Imperial College School of Medicine, Chelsea and Westminster Hospital Campus, 369 Fulham Road, London SW10 9NH, UK*

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Neuropathic pain is defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system'.[94] The spectrum of neuropathic pain covers a variety of disease states (Table 1) and presents in the clinic with a variety of symptoms.[145] Neuropathic pain is often reported as having a lancinating or continuous burning character and is often associated with the appearance of abnormal sensory signs, such as allodynia (pain as a result of a stimulus which does not normally provoke pain) or hyperalgesia (an increased response to a stimulus which is normally painful) (Figure 1). The sensory phenomena can be further characterized into static or dynamic sub-types. The mechanistic implication of allodynia is that elements of the sensory nervous system, which normally signal innocuous sensation have begun to encode painful stimuli, whilst in hyperalgesia the structures that sub-serve nociception have become hyperexcitable. Neuropathic pain is an area of largely unmet therapeutic need. The current pharmacological mainstays of clinical management are tricyclic anti-depressants and certain anti-convulsants,[92] [119] but these only achieve clinically significant (greater than 50%) pain relief in less than 50% of patients and are associated with sub-optimal side effect profiles. Opioids are generally considered to be less effective in neuropathic pain than in inflammatory pain, with the dose response curve of opioids in neuropathic pain shifted to the right of that for inflammatory pain, although the extent of this difference is controversial.[112]

The majority of research into neuropathic pain mechanisms has concentrated on changes in the peripheral nerve or spinal cord after peripheral nerve injury and, therefore, most available evidence relates to changes in these parts of the nervous system and the review will, therefore, focus on these aspects. Nevertheless, it is important to recognize that alterations in the brain have also been demonstrated following peripheral nerve injury, but much less is known about the significance of these changes. For example, phantom limb pain has been shown to be associated with re-organization of the cortex of humans.[43] The degree of cortical re-organization, as determined by BTi neuromagnetic imaging, was linked in a linear fashion to the intensity of pain, with an increase in re-organization being associated with greater pain intensity.[43] A more recent study indicated that cortical re-organization was evident only in patients with phantom limb pain, and not in patients with non-painful phantom limb phenomena or congenital absence of the limb.[44]

Animal models

In order to identify novel therapeutics for neuropathic pain and, in particular, to design compounds for clinical use in 'mechanism based' treatment paradigms it is important to understand the underlying pathophysiology. Unlike inflammatory pain, human volunteer models of neuropathic pain have yet to be developed and animal models are, thus, the mainstay of such research and aspects of these models will be reviewed before a discussion of neuropathic pain mechanisms. Nevertheless, there are a number of shortcomings of these animal models, which need to be considered. In common with all animal models of pain, it is difficult to know what is actually perceived by the animal. However, for neuropathic models, a further drawback is that, in general, alterations in cutaneous sensory thresholds in response to a peripheral nerve injury rather than integrated pain-related behaviour are measured. Therefore, a priority is to develop neuropathic pain models, which also

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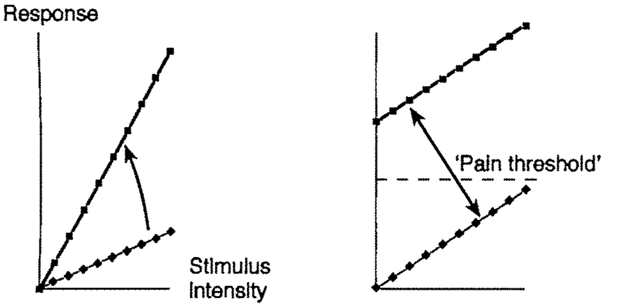
Table 1 Traditional aetiological classification of neuropathic pain, with examples. In the future, it is possible that this classification may be superseded by symptom or mechanism-based approaches to clinical management. An estimate of the prevalence, in the USA (population 270 million) is given in brackets after each example cited

Trauma: phantom limb (50), spinal cord injury (120).
Ischaemic injury: central pain (30), painful diabetic neuropathy (600).
Infection/inflammation: post-herpetic neuralgia (500), HIV (15).
Cancer: invasion/compression of neural structures (200).
Drugs: vinca alkaloids.
Compression: sciatica (2100), trigeminal neuralgia (15).
Unknown: trigeminal neuralgia, MS (51).



(A) Hyperalgesia
– An increased response to a normally painful stimulus

(B) Allodynia
– A painful response to a normally innocuous stimulus

Fig 1 Graphical representation of hyperalgesia and allodynia: stimulus intensity *vs* response relationship for noxious and innocuous stimuli.

feature a measurable and repeatable 'integrated behavioural pain response'. Furthermore, whilst neuropathic pain is a devastating response to nerve injury, it is not the usual consequence, as most patients do not develop neuropathic pain following nerve injuries. However, animal models have been developed to result in a highly reproducible and frequent development of allodynia and hyperalgesia and this does not mirror the 'normal' human response to nerve injury. It is, therefore, important to identify the injury and patient factors that dictate whether a human develops pain in response to nerve injury. Finally, for good ethical reasons, most animal models of neuropathic pain study the animals for a period of weeks, whereas the clinical course of neuropathic pain presenting to a pain relief clinic is years.

With these caveats in mind, we must first survey the various animal models of neuropathic pain that have been developed, with simple axotomy being the first widely used model.[138] In this model, the self-mutilation of the injured foot (autotomy) was often observed and interpreted as a response to pain, the authors suggesting an afferent barrage from the neuroma as being crucial in generating autotomy behaviour. More recently, it has been suggested that autotomy occurs in response to the total motor and sensory denervation of the hind-paw rather than pain (for review see[63]). Ethical considerations dictate that autotomy is undesirable as an outcome measure and it is a very rare occurrence with the more recent neuropathic models.

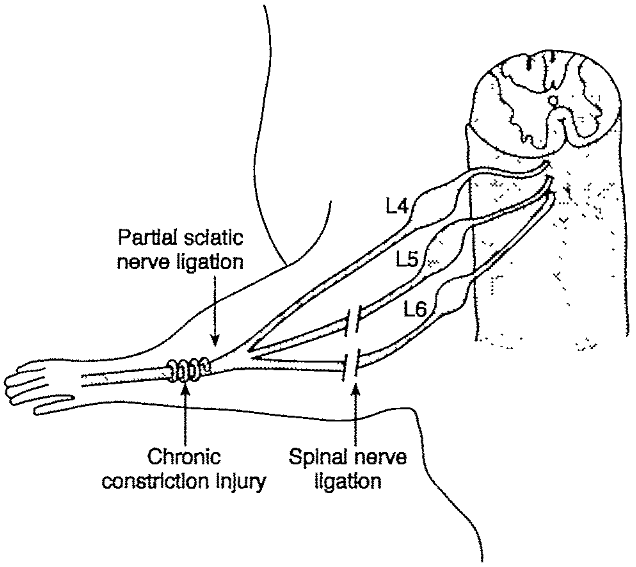


Fig 2 Schematic drawing of the partial sciatic nerve ligation (tight ligation of 33–50% of the sciatic nerve trunk), CCI (loose ligations of the sciatic nerve trunk), and SNL (tight ligation and transection of the L5 and L6 spinal nerves) animal models of neuropathic pain.

The majority of currently used neuropathic pain models share alterations in hind-limb cutaneous sensory thresholds following partial injury of a peripheral (usually sciatic) nerve as a common feature. In particular, demonstration of hyperalgesia to noxious thermal stimuli and allodynia to cold and mechanical stimuli are used as outcome measures. The three most commonly used models are the chronic constriction injury (CCI) of sciatic nerve,[10] the partial sciatic nerve ligation model (PNL)[116] and the spinal nerve ligation model (SNL)[66] (Figure 2).

The CCI model consists of the loose ligation of the sciatic nerve at mid-thigh level with chromic gut sutures.[10] An inflammatory reaction develops in response to the catgut and consequentially a loss of most A-fibres and some C-fibres, but few cell bodies.[129] This is associated with spontaneous pain-related behaviour, allodynia and hyperalgesia. It has been demonstrated that anti-inflammatory treatments of CCI rats decreases the associated thermal hyperalgesia[135] and so it is speculated that there is a significant inflammatory component in the development of the painful neuropathy. There is a degree of operator variability with this model, particularly in relation to the difference in the tightness of the ligatures. The PNL model also consists of injury to the sciatic nerve at mid-thigh level. In this model, a tight ligation is created around 33–50% of the sciatic nerve, leaving the rest of the nerve 'uninjured'.[116] This is associated with the development of spontaneous pain-like behaviour, allodynia and hyperalgesia. Although this model is regarded as having less of an inflammatory component than the CCI model, there is still likely to be variability in the actual number of ligated neurones per animal. Also, it is not easy to relate the PNL injury to a specific DRG or level of the spinal cord as it will be a random mixture of L4 and L5 spinal nerve afferents which are injured. The SNL model consists of injury to the L5 and L6 spinal nerves, which contribute to the sciatic nerve.[66] Once again, this is associated with the development of spontaneous pain-like behaviour as well as long lasting allodynia and hyperalgesia. The authors demonstrated that a tight ligation of the L5 spinal nerve only resulted in comparative symptoms to the L5 and L6 ligation group and hence some experimenters now use this as a modified SNL model.[15] This model is conducive to examination of cellular responses to the injury at the DRG level as the L5 and L6 DRGs will be affected, but the L4 DRG will not, and this allowed investigation into the importance of input from uninjured afferents in neuropathic pain.[80]

A direct comparison of these three models has been reported.[65] In this study, the authors demonstrated a similar onset of sensory threshold changes in mechanical and cold allodynia in all three models, but a greater magnitude of change in sensory thresholds in SNL. All three models demonstrated significant cold and mechanical allodynia at 3 days after injury and spontaneous pain at one day after injury. Mechanical allodynia was determined by the application of an 8.4 mN Von Frey hair. The allodynia was greatest in the SNL model with an ~80% response frequency, followed by PNL (~60% response frequency) and CCI (~45% response frequency). They also demonstrated a more significant involvement of the sympathetic nervous system component in the sensory response to SNL than following PNL or CCI.

A more recent development of the hind-limb peripheral nerve injury models has been a description of the sequelae of injury to the terminal branches of the sciatic nerve. Decosterd and Woolf described a spared nerve injury model involving tight ligation and lesion of the tibial and common peroneal nerves, leading to robust sensory threshold changes to mechanical, thermal, and cold stimuli.[28] Further studies investigated more closely the importance of injury to each branch in the development of behavioural signs of neuropathy, namely mechanical and cold allodynia and spontaneous pain.[75] This study demonstrated that the largest change in sensory thresholds was initiated by injury to the tibial and sural nerves, leaving the common peroneal nerve intact. This model allows testing of distinct regions of the hind-paw which are either innervated by injured or uninjured neurones, as well as separating degenerating neurones from uninjured neurones to a greater level. A further model exploiting injury to the sciatic nerve is a photochemical/laser irradiation model. The sciatic nerve is subjected to an ischaemic injury as a result of laser activation of a systemically administered photosensitive dye resulting in a thrombosis within the nerve because of a photochemical reaction. This model was originally described for the study of direct spinal cord injury[150] before being adapted to become a peripheral nerve injury model.[73] This model has been described as having good reproducibility statistics, as well as a quantifiable degree of nerve injury. However, this model has not been widely adopted, presumably because of the expenses of lasers.

The majority of animal models of neuropathy have been based on a discrete peripheral nerve injury. However, some have been developed to more closely mimic individual disease states. An example of this is the streptozotocin model of peripheral diabetic neuropathy.[85] In this model, a single injection of streptozotocin induces diabetes and then hyperalgesia and allodynia. This model has been used extensively in the testing of new pharmaceuticals such as gabapentin,[41] however, the influence of the ill health of the rats *per se* (as opposed to neuropathy) on sensory thresholds has been questioned.[45] A further example, described by Idanpaan-Heikkila and Guilbaud, uses a CCI of the infraorbital branch of the trigeminal nerve as a model for trigeminal neuralgia.[58] A model of acute herpes zoster has been reported, which may offer some insight into the mechanism of acute zoster pain and possibly post-herpetic neuralgia.[42] Takasaki and colleagues have also demonstrated that, in comparison with herpes simplex in humans, herpes simplex virus type-1 induces allodynia and hyperalgesia in infected rats.[128]

The majority of neuropathic pain models were originally described in rats, but more recently the PNL model has been adapted to the mouse,[86] as has the photochemically induced ischaemia model.[51] The translation of these models from rat to mouse is important as novel transgenic tools, useful for the study of neuropathic pain, are developed further. However, mice are not merely small rats and often respond in a quantitatively and qualitatively different manner to an insult, and the translation of pain models from rats to mice is more than simply an adaptation of surgical techniques. Other developments in genetics could be exploited to enhance understanding of painful neuropathy. For example, one such approach described the induction of mutants identified in inherited peripheral neuropathies into mice.[89]

Mechanisms of neuropathic pain

A variety of pain-related phenomena, both central and peripheral, have been associated with peripheral nerve injury (Fig. 3). These are generally not mutually exclusive and it is entirely possible that any one of these (or more likely a combination) contribute to symptomatology in individual patients suffering from neuropathic pain. It is, therefore, inappropriate to attempt to generate a unifying hypothesis of pathophysiology for all neuropathic pain states. The next challenge is to diagnose which of these phenomena may be operative in an individual patient and to interpret each symptom within the mechanistic framework arising from work with neuropathic pain models. In this regard, neuropathic pain is ideally suited to the mechanistic based treatment of chronic pain recently proposed.[145]

Peripheral mechanisms

Ectopic discharges and ephaptic conduction

In normal primary afferent neurones, it is rare for firing threshold to be reached without the input of a stimulus. However, following a nerve injury, it has been demonstrated that there is a large increase in the level of spontaneous firing in the afferent neurones linked to the injury site (Fig. 4).[139] This has been termed ectopic discharge and has also been demonstrated in humans, suffering from neuropathic pain. A microneurographic investigation of phantom limb pain patients examined the site of origin of the ectopic discharge and demonstrated that whilst the pain and discharge evoked by tapping the neuroma were locally initiated, the spontaneous pain and discharge were not.[99] However, there has been criticism of the techniques used to glean this information.[110] Because of the practical problems of recording from humans, most of the studies have been carried out in animal models. Ectopic discharges were originally described as arising in the neuroma itself.[139] However, further studies revealed that some ectopic discharges could also originate from the DRG and other points along the nerves.[137] Having demonstrated the presence of ectopic firing in peripheral nerve injury animal models, as well as in human patients, it is important to investigate the cause of these discharges.

Peripheral effect	Central effects
• Ectopic and spontaneous discharge • Ephaptic conduction • Alterations in ion channel expression • Collateral sprouting of primary afferent neurones • Sprouting of sympathetic neurones into the DRG • Nociceptor sensitization	• Central sensitization • Spinal reorganization • Cortical reorganization • Charges in inhibitory pathways

Fig 3 Summary of the phenomena which have been observed in the central and peripheral nervous system after experimental peripheral nerve injury, which may contribute to neuropathic pain.

A small number of A-fibres (10%) exhibit sub-threshold membrane oscillations in their resting state or under depolarization conditions.[81] Following SNL, this was seen to increase to 23% at 9 days post-operation. A similar increase in membrane oscillations of both A- and C-fibres was also seen by Amir and colleagues.[5] This increased oscillatory behaviour leads to an increase in ectopic firing as the oscillations more frequently reach threshold and subsequent 'cross-excitation' of other neurones serves to amplify this effect. As the DRG neurones are all effectively isolated from each other, cross-talk or ephapsis is unlikely to normally occur within the DRG and does not do so after

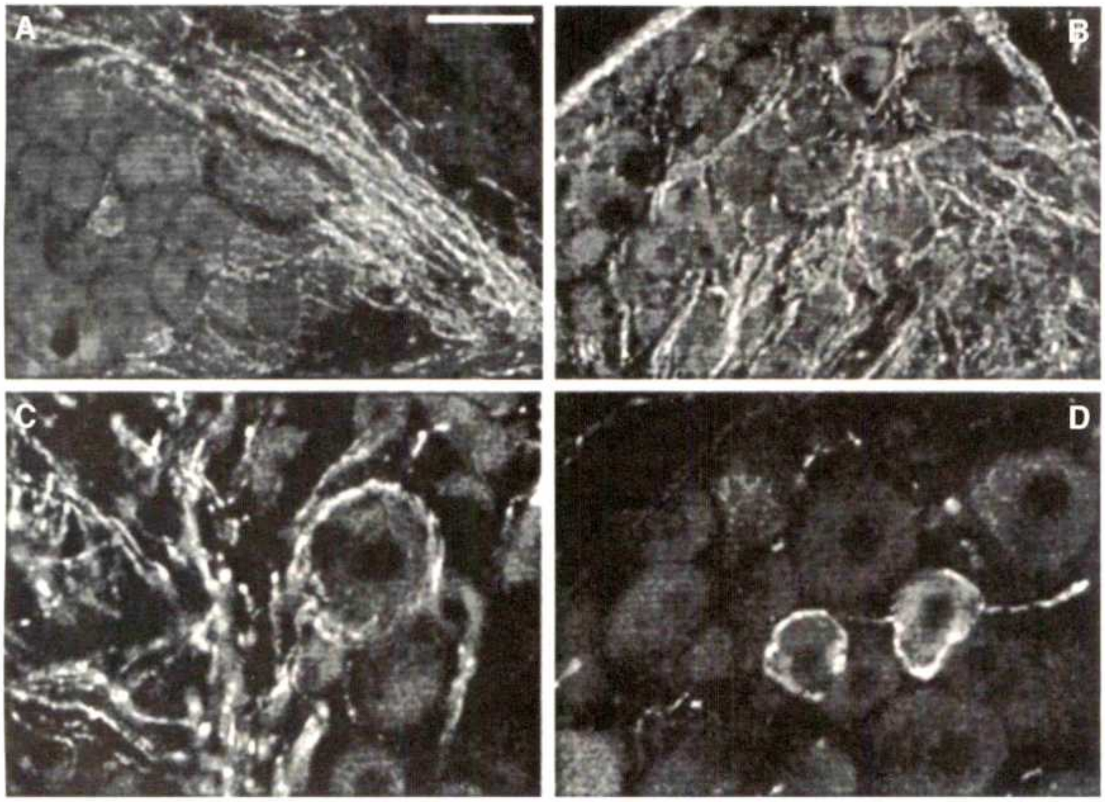


Fig 4 Tyrosine hydroxylase immunoreactivity within the DRG showing post-ganglionic sympathetic fibre invasion after sciatic nerve axotomy (A) and intrathecal administration of NGF (B). Higher power magnification shows the distinct 'basket' structures surrounding sensory cell bodies (C), (D) Adapted from Jones and colleagues.[62]

Table 2 Summary of the properties of those sodium channels preferentially expressed by primary sensory neurones and how these properties alter after inflammation or peripheral nerve injury. *NB redistribution from DRG

	TTX sensitivity	**Normal DRG expression**	**Growth factor dependence**	**Inflammation**	**Neuropathy**
SNS2/ NaN	Resistant	Yes	GDNF	↑	↓
III	Sensitive	No	?	X	↑
SNS/ PN3	Resistant	Yes	NGF	↑	↓*

nerve injury.[34] However, chemically mediated cross-excitation has been shown to occur in the DRG.[3] Cross-depolarization has been demonstrated to occur following tetanic stimulation in most (90%) neurones within the DRG.[134] This depolarization is transient following neighbouring cell stimulation and is sub-threshold for eliciting an action potential.[3] However, as has been discussed, following peripheral nerve injury, many DRG neurones exhibit alterations in their membrane potential to bring them closer to the firing threshold. It is, therefore, possible that the cross-excitation will then be sufficient to evoke ectopic firing. It is important to note that there is no increase in the level of cross-excitation itself in response to nerve injury, just in the excitability of the DRG.[82] A more recent study has demonstrated evidence of cross-excitation between A- and C-fibres.[4]

These observations suggest that the development of ectopic activity may be particularly important for the development of hyperalgesia, allodynia and ongoing pain associated with nerve injury. Clinical observations suggest that ectopic activity is responsible for ongoing neuropathic pain.[49] It is now recognized that two populations of afferent fibres develop ectopic activity following nerve injury, the injured sensory neurones themselves and their uninjured neighbours.[48] To what degree each population is responsible for the maintenance or initiation of neuropathic pain is currently under debate. Support for a major role of injured afferents comes from the work of Sheen and Chung[117] who used the SNL model of neuropathic pain, ligation of the L5 and L6 spinal nerves. They reported that cutting the dorsal roots of injured segments eliminated pain behaviours. Three other recent studies have demonstrated a direct correlation in the time course of behavioural changes following spinal nerve injury with that of ectopic activity in A-fibres that gives support to the 'injured afferent' hypothesis.[67 82 83] Note that changes in ectopic C-fibre activity only occur 3–4 weeks following axotomy and may persist for many weeks following injury.[31]

Evidence has also been obtained that signals in uninjured neighbouring afferents have a role in the development of neuropathic pain behaviours. Using a modified spinal SNL model, Yoon and colleagues[154] and Li and co-workers[80] showed that an L4 rhizotomy would abolish pain behaviours evoked by L5 SNL. This suggests that the signals involved in pathological nociception arise from the intact neurones. It is important to bear in mind, therefore, that pain arising as a result of peripheral nerve damage may reflect activity in both damaged as well as intact sensory neurones.

Sodium channels are critical to the physiology of excitable membranes, including neuronal membranes. One important finding of potential significance to the generation of ectopic firing is alterations in the expression of sodium channels in the cell bodies and the terminal neuroma of peripheral nerves following nerve injury (summarized in Table 2). In 1989, Devor and colleagues demonstrated the accumulation of Na^+ channels in the neuroma of cut sensory axons[32] and then demonstrated that the Na^+ channels were the cause of ectopic discharge.[90] However, molecular biology has since revealed that are many different and distinct voltage-gated Na^+ channels, of which at least six are expressed on the cell bodies of primary afferent neurones within the DRG.[141] These can be further split into tetrodotoxin (TTX)-sensitive and TTX-resistant sub-types. TTX-sensitive channels are expressed throughout the central nervous system, and predominantly in A-fibres within the DRG. TTX-resistant channels are found only within a subset of primary afferent neurones of the DRG, specifically in the smaller C-fibres associated with nociception.[2] Following peripheral nerve injury, it has been demonstrated that there is a re-organization of the nature and levels of expression of the various channels.[142] The expression of some sodium channels sub-types in DRG cell bodies is diminished following nerve injury, whilst others appear *de novo* and others translocate to different parts of the neurone. More specifically, there is an up-regulation of type III TTX-sensitive channel gene expression (these are not normally expressed by DRG cells),[142] and a down-regulation of SNS (aka PN3) and NaN (aka SNS2) TTX-resistant channels gene expression.[36] This has been demonstrated to occur both after axotomy[36 142] and after CCI with a 40% decrease in SNS and NaN mRNA after CCI.[37] The SNS channel expression appears to translocate from the cell body to the neuroma, which may explain the hypersensitivity of the neuroma. These findings were corroborated in an immunohistochemical study (for NaN and SNS) of tissue taken from patients suffering from chronic neuropathic pain after traumatic brachial plexus avulsion.[24] Another study investigated the changes in SNS/PN3 and SNS2/NaN TTX-resistant Na^+ channels in injured human sensory nerves.[153] This demonstrated degradation products of the

SNS2/NaN and an increase in SNS/PN3 expression in injured nerves localized close to the injury site and within the neuroma.

There is also supportive evidence for these findings from electrophysiological studies. Cummins and Waxman demonstrated that, after axotomy of the sciatic nerve, there was a reduction in the density of TTX-resistant currents within the DRG.[26] This study also demonstrated no increase in TTX-sensitive current density after axotomy, but an increase in the repriming speed of these currents, up to four times faster. Similar experiments in the CCI model of neuropathy demonstrated the same reduced density of TTX-resistant currents, and also demonstrated a shift in the voltage dependence of activation to a more negative potential.[37 72]

The mechanism contributing to the changes in Na^+ channel expression in peripheral nerve injury is unclear, but neurotrophin supply appears to be a crucial factor. It has been shown that DRG neurones in culture will increase expression of type III channel expression and decrease SNS channel expression in the absence of NGF.[13] NaN channel expression is similarly reliant on another growth factor, for example, glial-derived neurotrophic factor (GDNF). It seems clear that the decrease in SNS2/NaN expression, the relocation of SNS/PN3 channel expression and the *de novo* synthesis of type III channels are central in the spontaneous generation of action potentials. These changes in DRG following peripheral nerve injury suggest a contribution to neuronal hyperexcitability from sodium channels and this Na^+ channel-induced hyperexcitability is likely to manifest itself as an increase in ectopic firing, because of the rapid repriming and lower resting thresholds. It is likely that the rapidly repriming, normally silent, type III TTX-sensitive channel has a significant role to play in this, and this is supported by low dose TTX studies. Omana-Zapata and colleagues demonstrated in axotomized rats that i.v. TTX produced dose-dependent inhibition of ectopic activity.[100] Similarly, Lyu and colleagues demonstrated that topically applied, at the DRG level, sub-action potential blocking levels of TTX reduced mechanical allodynia in the SNL model.[84] The sodium channel blocker lidocaine has also been demonstrated to be of some benefit in neuropathic pain treatment,[8] but currently available sodium channel blockers do not, by and large, discriminate between the different types of channel and are, therefore, associated with potentially lethal side-effects. Tailoring novel compounds to specifically act at the sodium channels implicated in neuropathic pain may represent a significant therapeutic advance.

Sodium channels are not the only voltage-gated channels, which are altered following peripheral nerve injury. Calcium channels have also been shown to influence the generation of hyperalgesia and allodynia. Specific antagonists for neuronal N-type Ca^{2+} channels have been shown to reduce heat hyperalgesia and mechanical allodynia in the CCI model when administered directly to the site of nerve injury.[149] Further studies then demonstrated that subcutaneous administration of an N-type, but not P- or Q-type, Ca^{2+} channel antagonist attenuated mechanical hyperalgesia in the PNL model of neuropathic pain, suggesting a local effect of N-type Ca^{2+} channels in the generation of hyperalgesia.[143] This alteration of Ca^{2+}currents after peripheral nerve injury has also been demonstrated electrophysiologically.[7] More specifically, N-type current measured in the DRG was seen to decrease after axotomy, with no significant change in P- or Q-type currents. Cannabinoids CB_1 receptor agonist attenuate Ca^{2+} flux at N-type channels[103] and we have recently demonstrated that the synthetic cannabinoid Win 55,212–2 attenuates thermal hyperalgesia and mechanical and cold allodynia in the SNL model of painful neuropathy via the CB_1 receptor.[15] Furthermore, the anti-convulsant gabapentin binds to the $\alpha_2\delta$ sub-unit of calcium channels[46 130] and is effective in relieving allodynia and hyperalgesia in animal models and neuropathic pain in man.[1 101 113]

The changes in both Na^+ and Ca^{2+} channels detailed above are important in neuropathic pain. The *de novo* synthesis of rapidly repriming III channels, down-regulation of TTX-resistant Na^+ channels and loss of high-voltage activated N-type Ca^{2+} channels seen in response to peripheral nerve injury, increases the excitability of the neurones. This in turn will lead to an increase in firing susceptibility and frequency, possibly resulting in not only spontaneous pain, but also central sensitization as discussed later.

Collateral sprouting

Sprouting of collateral fibres from sensory axons in the skin into denervated areas has been described following nerve crush injuries.[33] Sprouting was also observed from the saphenous nerve in the CCI model.[111] This sprouting occurred at around 10 days post-operation, but the degree of sprouting was not proportional to the degree of hyperalgesia after chronic sciatic section.[68] These results indicate that collateral sprouting is unlikely to contribute significantly to the pain behaviour seen in this model. The sprouting was effectively blocked by the administration of anti-NGF[35] and it is, therefore, likely that a local release of NGF from sources within the skin (keratinocyte, immune cells) is responsible for axon sprouting under these circumstances.

Coupling between the sympathetic nervous system and the sensory nervous system

Clinicians have observed for many years that in a small subset of patients suffering from neuropathic pain, the pain is somewhat dependent on activity in the sympathetic nervous system. This is often referred to as 'sympathetically maintained pain' and, for example, some patients suffering from complex regional pain syndrome type 1 (CRPS1) can be classified as having sympathetically maintained pain. It has recently been demonstrated that an abnormal contact develops between the sympathetic nervous system and the sensory nervous system following peripheral nerve injury, which may underlie the enhanced sensitivity to catecholamines which some patients with neuropathic pain develop.[61] The key question is how and where does the sympathetic nervous system become coupled to the sensory nervous system to produce the pain observed in the clinical situation? The basic observation must be that activity in the sympathetic nervous system initiates abnormal impulse traffic in sensory neurones that leads to pain perception. Several sites of coupling between sensory and sympathetic nervous systems have been proposed and tested in animal models. The following have received experimental support.

1. Direct chemical coupling within peripheral effector sites between the noradrenergic and sensory neurone terminals.[102]
2. Ephaptic nerve coupling. Observed between sensory fibres in a damaged nerve but not so far between sympathetic and sensory fibres.[14]
3. Indirect coupling via peripheral sensitizing mechanisms involving the release of inflammatory mediators from sympathetic terminals and the sensitization of primary sensory neurone axons.[78]
4. Direct coupling between the sympathetic nervous system and the sensory nervous system in the dorsal root ganglion.

This latter possibility has received much attention recently with numerous studies demonstrating that peripheral nerve injury leads to sympathetic sprouting in the DRG (Fig. 4). McLachlan and colleagues described sprouting of noradrenergic perivascular sympathetic axons into the DRG following ligation of the sciatic nerve.[91] These axons were observed to form baskets around the large diameter neurones, leading to the possibility of sympathetic input being able to activate the neurones. Sympathetic sprouting has also been demonstrated following SNL[19] and CCI[108] models. In the McLachlan study, onset of sprouting occurred around 21 days after nerve injury, whereas Chung and others described visualization of sympathetic sprouts after 3 days which was maintained for up to 20 days before declining gradually.[20] It should be noted that onset of behavioural signs of neuropathy in SNL are developed by 3 days post-surgery. This study also demonstrated elimination of the majority of sprouting following sympathectomy, confirming that the sprouts were sympathetic postganglionic fibres. A direct comparison of the sympathetic sprouting in CCI, PNL, and SNL was performed[76] and demonstrated a similar pattern of sprouting in CCI and PNL, with an onset after 2 weeks, but a more rapid onset of within 1 week of SNL.

The mechanism for onset of the sympathetic sprouting is unclear. It is likely, however, that neurotrophic factors and cytokines linked to Wallerian degeneration are crucial to the process. Wallerian degeneration results in an increase of a large variety of cytokines and growth factors in the local milieu. Thompson and Majithia demonstrated the ability of the cytokine leukaemia inhibitory factor (LIF) to stimulate sympathetic sprouting, akin to that seen in peripheral nerve injury, in non-nerve injured animals.[132] In previous studies, the neurotrophin nerve growth factor (NGF) has been demonstrated as being able to induce sympathetic sprouting in the CNS[59] and this led to the investigation of the role of NGF, and GDNF, in sympathetic sprouting in DRG.[62] This study demonstrated that exogenously applied NGF, but not GDNF, to uninjured rats resulted in sympathetic sprouting reminiscent of that in CCI rats. Also demonstrated, was that sequestration of endogenous NGF at the injury site did not reduce sprouting. This suggests a mechanism of sprouting involving the direct action of NGF at the level of the DRG, a theory supported by raised NGF mRNA levels in the DRG following sciatic nerve injury.[115] These studies have proposed some potential mechanisms for sympathetic sprouting in the DRG (see[109] for review).

Sprouting has been described in many animal models of peripheral nerve injury, but what are the consequences of such sprouting? The terminals of the sprouted neurones have been shown to form functional synapse-like structures with the cell bodies.[91] These structures could be involved in the formation and maintenance of abnormal excitation arising from the DRG, a hypothesis supported by electrophysiological studies in which sympathetic stimulation increased sensory ectopic discharge from the DRG.[31] As both sympathectomy[118] and guanethidine,[98] a noradrenergic depleting agent, have been demonstrated to relieve hyperalgesia in peripheral neuropathy models, it is fair to assume that these functional interactions have some importance in the sympathetically maintained pain subgroups of neuropathic pain patients. Sympathetic blocks have been used in treatment of neuropathic pain,[148] although adequately controlled data are not available to help fully determine the efficacy of this approach. With the time-scale of sprouting corresponding with the onset of behavioural signs of both hyperalgesia and allodynia, block of the input from these fibres, or more difficultly, prevention of sprouting has potential to reduce sympathetically maintained pain in neuropathic patients.

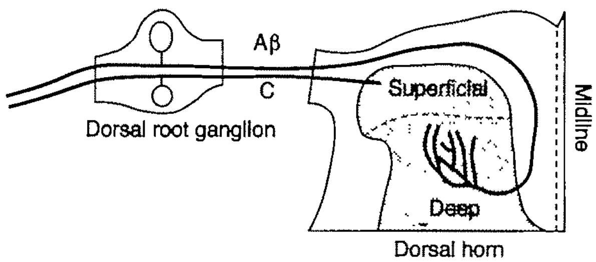
Bradykinin

There is an alteration in expression of bradykinin binding sites within dorsal root ganglion neurones after axotomy.[104] Bradykinin has been shown to play an important role in the hyperalgesia associated with inflammatory pain states.[39 60] Petersen and colleagues showed an increase in bradykinin binding sites at 2 days post-axotomy, suggesting a potential role for bradykinin antagonists in the treatment of neuropathic pain, specifically to combat hyperalgesia.[104]

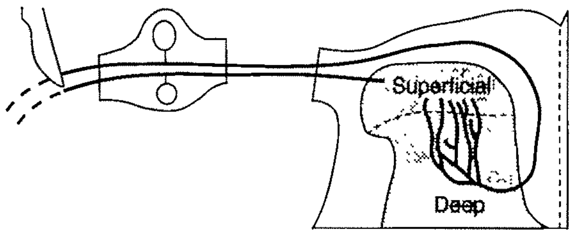
Central mechanisms

Spinal cord—anatomical re-organization

There is a considerable degree of re-organization of spinal cord in response to peripheral nerve injury (Fig. 5). Under normal physiological conditions, different classes of



Normal terminations of primary afferents in the dorsal horn



After nerve injury, C-fibre terminals atrophy and A-fibre terminals sprout into the superficial dorsal horn

Fig 5 Schematic representation of reorganization of the spinal dorsal horn which is observed after peripheral nerve injury. After the peripheral nerve injury the unmyelinated primary afferent neurones which normally sub-serve nociception and terminate in the superficial dorsal horn degenerate. This allows the larger myelinated primary afferent neurones, which normally sub-serve innocuous sensory modalities, to sprout into the superficial dorsal horn from the laminae deeper in the dorsal horn which normally receive their central terminations. This observation allows some insight into the mechanisms of allodynia. (Adapted with permission from Woolf and Mannion.[145])

primary afferent neurone fibres terminate in specific laminae of the dorsal horn. As a generalization, the nociceptive small diameter cells with myelinated Aδ-fibres and unmyelinated C-fibres terminate in the superficial laminae (I and II) of the dorsal horn whilst the large diameter neurones with myelinated Aβ-fibres terminate in laminas III and IV. Lamina V is a region of convergence of inputs. Woolf and colleagues demonstrated that after sciatic nerve axotomy, the central terminals of the large myelinated primary afferent neurones sprouted into lamina II of the superficial horn.[146] Koerber and colleagues also showed a sprouting of Aβ-fibres into lamina II of the superficial dorsal horn after peripheral axotomy.[69] Woolf and co-workers then demonstrated that this sprouting occurred within 1 week post-axotomy, was at its highest 2 weeks post-axotomy and persisted over 6 months post-axotomy.[147] The authors also demonstrated that this sprouting persisted beyond periods of peripheral nerve regeneration. One consequence of this synaptic rearrangement is that second-order neurones within the spinal cord, that normally receive predominantly high-threshold sensory input, begin to receive inputs from low-threshold mechanoreceptors. This misinterpretation of information within the spinal cord may result in low-threshold sensory information being interpreted as nociceptive, thus, providing another explanation for the emergence of allodynia after peripheral nerve injury.

The mechanisms responsible for this sprouting have been investigated. Bennett and colleagues investigated whether the intrathecal administration of either NGF, NT-3, or BDNF after sciatic nerve axotomy prevented such sprouting.[9] It was observed that NGF, but not NT-3 or BDNF was able to prevent the sprouting of the Aβ-fibres into lamina II.[9] Coupled with a study demonstrating that C-fibre degeneration after treatment with capsaicin was associated with a pattern of staining of Aβ sprouting indistinguishable from that of axotomy,[87] the authors concluded that the rescue of C-fibres by NGF was responsible for the prevention of Aβ sprouting. By inference, the normal retrograde supply of NGF to the cell body was necessary to maintain the normal laminar distribution of terminals within the spinal cord. Complete sciatic nerve axotomy does not result in the same pattern of hyperalgesia or allodynia observed in other animal models of neuropathic pain. As a result, Lekan and colleagues investigated the Aβ-fibre sprouting in the SNL model of neuropathic pain and established a robust sprouting of Aβ-fibres at 2 and 4 weeks post-surgery,[77] suggesting a similar mechanism to the axotomy studies. However, one note of caution needs to be considered when interpreting these sprouting studies. Hökfelt and colleagues demonstrated that the marker (cholera toxin β sub-unit) used to selectively image Aβ-fibres may also be taken up by C-fibres after peripheral nerve injury, but the full significance of this finding remains to be elucidated.[133]

The functional significance of this sprouting needs to be considered. C-fibres normally innervate lamina II and are responsible for nociceptive signalling, whilst Aβ-fibres are large fast conducting neurones that sub-serve low-threshold non-noxious inputs. Therefore, if the Aβ-fibres sprout into lamina II, and establish functional synaptic contact with second-order neurones, then low-threshold non-noxious inputs from the Aβ-fibres can be interpreted as nociceptive in origin. This would be a plausible explanation for allodynia, a hypothesis supported by electrophysiological data: recordings from dorsal horn neurones in a rat transverse spinal cord slice were examined. In normal rats, lamina II cells exhibited long-latency responses to high-threshold nerve stimulation. However, after sciatic nerve section, and subsequent sprouting of Aβ-fibres into lamina II, 54% of the activity in lamina II were initiated by low-threshold stimulation and the majority exhibited short-latency responses reminiscent of those in lamina III of normal rats.[70] However, it should be noted that optimal sprouting does not occur until 2 weeks post-injury and so cannot be solely responsible for the allodynia observed in neuropathy models.

Spinal cord—hyperexcitability

In a similar fashion to persistent inflammation, the afferent barrage associated with peripheral nerve injury is associated with the development of a sustained state of hyperexcitability of dorsal horn neurones, a process dubbed 'central sensitization'.[21 136] In addition to events such as lowering of activation thresholds of spinal neurones, central sensitization is characterized by the appearance of 'wind-up'.[93 140] (For review see[38].) Wind-up is characterized by an increasing response to repeated C-fibre volleys, and may contribute to hyperalgesia. However, the exact relationship of the relatively short lived phenomenon of wind-up and the persistent state of central sensitization remains to be fully elucidated.[79 144] Electrophysiological data demonstrated that about 90% of dorsal horn neurones studied in the lumbar enlargement of the spinal cord exhibited abnormal characteristics after CCI.[74]

Study of the pharmacology of central sensitization may open the door for novel analgesics effective in neuropathic pain. The excitatory amino acid glutamate is the major excitatory neurotransmitter released at the central terminals of primary afferent nociceptive neurones after noxious stimulation. Whilst glutamate acts at a number of post-synaptic receptors, a large body of evidence suggests that the ionotropic NMDA sub-type is the most intimately involved in both inflammation and nerve injury-induced central sensitization (see[38]). Removal of an Mg^{2+} dependent ion channel block and receptor phosphorylation are critical events in 'activating' the NMDA receptor so that glutamate is able to exert its effects. NK1 (substance P), AMPA (glutamate), and trkB (BDNF) receptors are all involved in this permissive process.[131]

A number of lines of evidence suggest that NMDA receptor antagonists may have a role in attenuating features of neuropathic pain. First, glutamate concentration increases in the ipsilateral dorsal horn after CCI.[64] Davar and colleagues described the prevention of hyperalgesia development in the CCI model by continual pre- and post-injury i.p. administration of the NMDA receptor antagonist MK-801.[27] Mao and others described a reduction in hyperalgesia in the same model at a lower dose of MK-801 and also demonstrated the dose-dependent anti-hyperalgesic effect of intrathecally administered MK-801 3 days post-injury.[88] Electrophysiological data also demonstrates that MK-801 significantly reduces the hyper-responsiveness to noxious stimulation after peripheral nerve injury.[123] Interestingly, the authors found that MK-801 had no effect on the frequency of ectopic baseline firing (spontaneous pain), suggesting that this is not mediated through central NMDA receptors.

Glycine is recognized as a modulator of the agonist action of glutamate at the NMDA receptor.[23] This has led to investigation of the anti-nociceptive effects of antagonists to the glycine modulatory site of the NMDA receptor. Quartaroli and colleagues described the efficacy of a glycine site antagonist in preventing the development of hyperalgesia in the CCI model and attenuating wind-up in isolated spinal cord neurones.[106] Co-administration of a glycine/NMDA receptor antagonist and morphine has also been demonstrated to attenuate pain behaviour in an animal model of trigeminal neuralgia.[18] In human neuropathic pain, ketamine, an NMDA receptor antagonist has been used to successfully treat neuropathic pain in some patients,[107] suggesting a place in therapy for NMDA antagonists and an area in which more investigation should be performed.

The mechanism by which NMDA receptors contribute to maintenance of central sensitization should also be discussed. After peripheral neuropathy, both an increase in excitatory amino acids and $[Ca^{2+}]_i$ were observed to occur in an NMDA receptor dependent manner.[64] This suggests that initial NMDA receptor activation contributes to the increased levels of glutamate and aspartate, representing a continual positive feedback loop which maintains sensitization. The increased $[Ca^{2+}]_i$ could also form a positive feedback loop, potentially through indirect activation of protein kinase C (PKC), a hypothesis supported by the anti-allodynic effect of a PKC inhibitor in the SNL model of neuropathic pain.[56]

The γ-aminobutyric acid (GABA) pathway forms a major inhibitory neurotransmitter system in the CNS. Suppression of this pathway by the $GABA_A$ receptor antagonist bicuculline is associated with a dose-dependent allodynia[152] and GABA receptor levels in the spinal cord are decreased within 2 weeks of sciatic nerve axotomy,[17] probably as a result of degeneration of the primary afferent neurone terminals on which the receptor is localized.[16] This suggests a role for GABA in modulating the response to peripheral nerve injury, and Sivilotti and Woolf hypothesized that central sensitization might be contributed to by a decrease in the efficacy of GABA pathways.[120] The $GABA_B$ agonist baclofen is anti-nociceptive in naïve animals, but its potency increases 3-fold in the CCI model of neuropathic pain.[121] More recently, Hwang and Yaksh demonstrated a dose-dependent attenuation of SNL associated allodynia, mediated via both $GABA_A$ and $GABA_B$ receptors, after intrathecal administration of GABA receptor agonists.[57] Stiller and colleagues were able to measure the concentration of extracellular GABA concentrations in normal and nerve injured rats and established a significant decrease in extracellular GABA concentrations in the nerve injured rats exhibiting allodynia, but a much smaller decrease in non-allodynic rats.[126] They then demonstrated that spinal cord stimulation, a potential therapy in humans, increased the levels of GABA in allodynic rats and that this in turn attenuated the release of EAA's in the dorsal horn.[25] These studies again indicate a role for decreased efficacy of GABA pathways in neuropathic allodynia.

A separate inhibitory pathway in the CNS is that of the purinergic system, including specifically adenosine. Adenosine exhibits both pre-[114] and post-synaptic actions and could produce anti-nociception by indirect interaction with EAA release.[22] Levels of circulating adenosine within the blood and CSF of neuropathic, non-neuropathic nerve lesioned and control humans were compared.[50] This study reported a significant decrease in circulating blood and CSF adenosine concentrations in neuropathic patients. From these data, coupled with the effective attenuation of

Inflammation	Nerve Injury
• Increased potency • Additional peripheral site of action • No increase in CCK expression	• Decreased potency • No peripheral effects • Loss of spinal receptors • Increased expression of CCK mRNA and CCK_b receptor

Fig 6 Mechanisms of opioid resistance in neuropathic pain: comparison of the effects of inflammation and nerve injury on features of the opioid system.

neuropathic pain seen after low-dose infusion of adenosine in a preliminary study,[122] a role of adenosine in modulating the development of neuropathic pain is a possibility.

Thus, there is evidence that a combination of increased activity in the excitatory and a concomitant decrease of activity in inhibitory systems within the spinal cord contributes to the phenomenon of central sensitization after peripheral nerve injury.

Endogenous opioid and cannabinoid systems

It is generally accepted that opioids are less effective in relieving neuropathic pain than inflammatory pain.[30] [112] Although, the exact extent of this is controversial, the balance of evidence supports the view of an unfavourable (right) shift in the dose response function for opioids in neuropathy. There are a number of plausible explanations for this observation, including a loss of peripheral opioid effects, loss of spinal opioid receptors and increased activity in physiological opioid antagonists systems (Fig. 6).

It is well established that a tertiary, peripheral site of opioid analgesia becomes operative during acute inflammation.[125] Not only are the immune components of this phenomenon unlikely to be operating during painful neuropathy to the extent that they are during inflammation, but peripheral nerve injury is associated with Wallerian degeneration and, therefore, a loss of axonally expressed opioid receptors. Zhang and colleagues demonstrated that peripheral axotomy was associated with a loss of μ-opioid receptors in both rat and monkey DRG.[155] Simultaneous to this down-regulation in μ-opioid receptors is an up-regulation in cholecystokinin (CCK) mRNA synthesized by neurones within the DRG.[151] CCK has opioid antagonistic properties[124] and so up-regulation will potentially further decrease the anti-nociceptive effects of opioids.

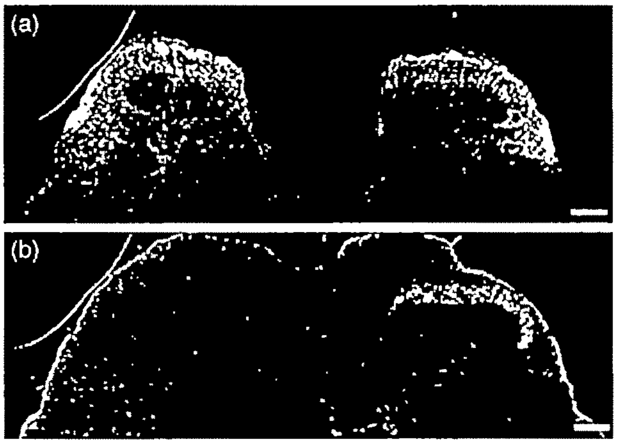


Fig 7 Preservation of cannabinoid CB_1 receptors in the dorsal horn after dorsal rhizotomy: sections A and B are transverse sections of rat lumbar spinal cord taken from animals which had undergone dorsal rhizotomy. Section A was immunostained for cannabinoid CB_1 receptors and there is no significant effect of dorsal rhizotomy. Section B was immunostained for the lectin IB4 (a marker of the GDNF dependent class of primary afferent nociceptor), the loss of IB4 staining ipsilateral to the dorsal rhizotomy indicates adequate degeneration of primary afferent nociceptors. After similar nerve injury, there is a considerable loss of μ-opioid receptor binding (scale bar 100 μm). Adapted from Farquhar-Smith and colleagues.[40]

In the spinal cord, opioid-receptors are localized predominantly on the pre-synaptic terminals of primary afferents in the superficial dorsal horn.[11] However, after peripheral axotomy, a decrease in immunocytochemical receptor staining has been reported[29] [155] and also after dorsal rhizotomy,[53] neonatal C-fibre degradation[54] and CCI[12] a decrease in μ-opioid receptor binding is observed, presumably reflecting the degeneration of primary afferent neurones as discussed above. However, in the SNL model, intrathecal administration of morphine produced greater inhibition of noxious stimuli generated electrophysiological responses than systemically administered morphine.[127] This suggests a potential role of spinally administered morphine where systemic morphine and other approaches have failed. Conversely, separate studies have demonstrated, immunocytochemically, an increase in μ-opioid receptors in the ipsilateral dorsal horn after CCI injury and a decrease after tight ligation of the sciatic nerve[47] whilst SNL injury caused little change in μ-opioid receptor binding or expression.[105]

As mentioned above, there is an increased expression of the endogenous opioid antagonist CCK mRNA after peripheral nerve injury. A corresponding increase in CCK_B receptor staining in the superficial dorsal horn has also been observed after peripheral axotomy. This appears to be related to increased synthesis of the receptor in the DRG which is then transported to the primary afferent central terminals the spinal cord.[6] It is possible that this increased level of inhibition on the opioid system contributes to decreased potency of opioids in neuropathic pain. This hypothesis was supported by a recent study in which morphine potency was enhanced in the SNL model by co-administration with a CCK_B receptor antagonist.[71]

Finally, recent advances in the understanding of cannabinoid analgesia[55] [103] appear to indicate a therapeutic advantage of cannabinoids over opioids in the management of painful neuropathy (Fig. 7). Cannabinoid CB_1 are located in areas of the spinal dorsal intimately associated with nociception.[40] In contrast, to the situation for spinal opioid receptors described above, no biologically relevant decrease in CB_1 receptor immunostaining was evident after dorsal rhizotomy suggesting a relative sparing of CB_1 receptors, compared with opioid receptors, after peripheral nerve injury[40] (Fig. 6). Similarly, using an alternative experimental approach, in which neonatal capsaicin treatment was used to deplete primary afferent C-fibres, Hohmann and Herkenham demonstrated only a modest decrease (~16%) of cannabinoid receptor binding in the superficial dorsal horn.[54] Meanwhile, μ-opioid receptor binding was considerably decreased (~60%) in the same region. In behavioural studies, cannabinoids have been shown to attenuate the sensory changes associated with CCI and SNL.[15 52]

Conclusion

This brief overview of the known mechanisms of neuropathic pain outlines the complex nature of the responses to a peripheral nerve injury. A unifying hypothesis of a single mechanism of all neuropathic pain is most unlikely to be proven and it is probable that an inter-related portfolio of mechanisms contribute to the generation of neuropathic pain in any given patient, with peripheral, spinal and brain events possibly all playing a role. Further elucidation of mechanisms underlying neuropathy will assist in developing novel targets for drug therapy.

Eventually, it may be possible to improve the ethos of clinical management protocols so that there will be a move away from the current disease based treatment towards symptom or, ultimately, mechanism based therapies, as suggested by Woolf and Mannion.[145] It is a clinical challenge to determine which mechanisms may be operating and hence responsible for individual symptomology in each patient. However, whilst a symptom-based approach is feasible it remains largely unevaluated in the clinic. Mechanism based therapy will require a better understanding of mechanisms involved in neuropathic pain and reliable convenient tools for their assessment in the clinic. Advances in our understanding of genetics may uncover genetic variation in the susceptibility of individuals to develop neuropathic pain after a nerve injury[96 97] and 'genetically tailor' analgesics based on an individual's pharmacogenetic profile.[95]

References

1 Abdi S, Lee DH, Chung JM. The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. *Anesth Analg* 1998; **87**: 1360–6

2 Akopian AN, Sivilotti L, Wood JN. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature* 1996; **379**: 257–62

3 Amir R, Devor M. Chemically mediated cross-excitation in rat dorsal root ganglia. *J Neurosci* 1996; **16**: 4733–41

4 Amir R, Devor M. Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. *Neuroscience* 2000; **95**: 189–95

5 Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999; **19**: 8589–96

6 Antunes Bras JM, Laporte A, Benoliel JJ, *et al.* Effects of peripheral axotomy on cholecystokinin neurotransmission in the rat spinal cord. *J Neurochem* 1999; **72**: 858–67

7 Baccei ML, Kocsis JD. Voltage-gated calcium currents in axotomised adult rat cutaneous afferent neurons. *J Neurophysiol* 2000; **83**: 2227–38

8 Bach FW, Jensen TS, Kastrup J, Stigsby B, Dejgard A. The effect of intravenous lidocaine on nociceptive processing in diabetic neuropathy. *Pain* 1990; **40**: 29–34

9 Bennett DL, French J, Priestley JV, McMahon SB. NGF but not NT-3 or BDNF prevents the A-fiber sprouting into lamina II of the spinal cord that occurs following axotomy. *Mol Cell Neurosci* 1996; **8**: 211–20

10 Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988; **33**: 87–107

11 Besse D, Lombard MC, Besson JM. Autoradiographic distribution of mu, delta and kappa opioid binding sites in the superficial dorsal horn, over the rostrocaudal axis of the rat spinal cord. *Brain Res* 1991; **548**: 287–91

12 Besse D, Lombard MC, Perrot S, Besson JM. Regulation of opioid binding sites in the superficial dorsal horn of the rat spinal cord following loose ligation of the sciatic nerve: comparison with sciatic nerve section and lumbar dorsal rhizotomy. *Neuroscience* 1992; **50**: 921–33

13 Black JA, Langworthy K, Hinson AW, Dib Hajj SD, Waxman SG. NGF has opposing effects on Na+ channel III and SNS gene expression in spinal sensory neurons. *Neuroreport* 1997; **8**: 2331–5

14 Blumberg H, Janig W. Activation of fibres via experimentally produced stump neuromas of skin nerve: ephaptic transmission or retrograde sprouting? *Exp Neurol* 1982; **76**: 468–82

15 Bridges D, Ahmad KS and Rice ASCR. The cannabinoid WIN 55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. Symposium on the Cannabinoids, International Cannabinoid Research Society; 2000: 117

16 Castro Lopes JM, Malcangio M, Pan BH, Bowery NG. Complex changes of GABAA and GABAB receptor binding in the spinal cord dorsal horn following peripheral inflammation or neurectomy. *Brain Res* 1995; **679**: 289–97

17 Castro Lopes JM, Tavares I, Coimbra A. GABA decreases in the spinal cord dorsal horn after peripheral neurectomy. *Brain Res* 1993; **620**: 287–91

18 Christensen D, Gautron M, Guilbaud G, Kayser V. Combined systemic administration of the glycine/NMDA receptor antagonist, (+)-HA966 and morphine attenuates pain-related behaviour in a rat model of trigeminal neuropathic pain. *Pain* 1999; **83**: 433–40

19 Chung K, Kim HJ, Na HS, Park MJ, Chung JM. Abnormalities of sympathetic innervation in the area of an injured peripheral nerve in a rat model of neuropathic pain. *Neurosci Lett* 1993; **162**: 85–8

20 Chung K, Lee BH, Yoon YW, Chung JM. Sympathetic sprouting in the dorsal root ganglia of the injured peripheral nerve in a rat neuropathic pain model. *J Comp Neurol* 1998; **376**: 241–52

21 Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–85

22 Corradetti R, Lo Conte G, Moroni F, Passani MB, Pepeu G. Adenosine decreases aspartate and glutamate release from rat hippocampal slices. *Eur J Pharmacol* 1984; **104**: 19–26

23 Corsi M, Fina P, Trist DG. Co-agonism in drug-receptor interaction: illustrated by the NMDA receptors. *Trends Pharmacol Sci* 1996; **17**: 220–2

24 Coward K, Plumpton C, Facer P, *et al.* Immunolocalization of

SNS/PN3 and NaN/SNS2 sodium channels in human pain states. *Pain* 2000; **85**: 41–50

25 Cui JG, O'Connor WT, Ungerstedt U, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. *Pain* 1997; **73**: 87–95

26 Cummins TR, Waxman SG. Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. *J Neurosci* 1997; **17**: 3503–14

27 Davar G, Hama A, Deykin A, Vos B, Maciewicz R. MK-801 blocks the development of thermal hyperalgesia in a rat model of experimental painful neuropathy. *Brain Res* 1991; **553**: 327–30

28 Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *Pain* 2000; **87**: 149–58

29 deGroot JF, Coggeshall RE, Carlton SM. The reorganization of mu opioid receptors in the rat dorsal horn following peripheral axotomy. *Neurosci Lett* 1997; **233**: 113–6

30 Dellemijn P. Are opioids effective in relieving neuropathic pain? *Pain* 1999; **80**: 453–62

31 Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. *J Neurophysiol* 1994; **71**: 38–47

32 Devor M, Keller CH, Deerinck TJ, Levinson SR, Ellisman MH. Na+ channel accumulation on axolemma of afferent endings in nerve end neuromas in Apteronotus. *Neurosci Lett* 1989; **102**: 149–54

33 Devor M, Schonfeld D, Seltzer Z, Wall PD. Two modes of cutaneous reinnervation following peripheral nerve injury. *J Comp Neurol* 1979; **185**: 211–20

34 Devor M, Wall PD. Cross-excitation in dorsal root ganglia of nerve-injured and intact rats. *J Neurophysiol* 1990; **64**: 1733–46

35 Diamond J, Holmes M, Coughlin M. Endogenous NGF and nerve impulses regulate the collateral sprouting of sensory axons in the skin of the adult rat. *J Neurosci* 1992; **12**: 1454–66

36 Dib Hajj S, Black JA, Felts P, Waxman SG. Down-regulation of transcripts for Na channel alpha-SNS in spinal sensory neurons following axotomy. *Proc Natl Acad Sci USA* 1996; **93**: 14950–4

37 Dib Hajj SD, Fjell J, Cummins TR, *et al.* Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. *Pain* 1999; **83**: 591–600

38 Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: State-dependent sensory processing, plasticity and the generation of pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. London: Churchill Livingstone, 1999; 165–82.

39 Dray A, Perkins M. Bradykinin and inflammatory pain. *Trends Neurosci* 1993; **16**: 99–4

40 Farquhar-Smith WP, Egertova E, Bradbury EJ, McMahon SB, Rice ASC, Elphick MR. Cannabinoid CB_1 receptor expression in rat spinal cord. *Mol Cell Neurosci* 2000; **15**: 510–21

41 Field MJ, Bramwell S, Hughes J, Singh L. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? *Pain* 1999; **83**: 303–11

42 Fleetwood-Walker SM, Quinn JP, Wallace C, *et al.* Behavioural changes in the rat following infection with varicella-zoster virus. *J Genet Virol* 1999; **80**: 2433–6

43 Flor H, Elbert T, Knecht S, *et al.* Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995; **375**: 482–4

44 Flor H, Elbert T, Muhlnickel W, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Exp Brain Res* 1998; **119**: 205–12

45 Fox A, Eastwood C, Gentry C, Manning D, Urban L. Critical evaluation of the streptozotocin model of painful diabetic neuropathy in the rat. *Pain* 1999; **81**: 307–16

46 Gee NS, Brown JP, Dissanayake VUK, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, Gabapentin (Neurontin), binds to the alpha2-delta subunit of a calcium channel. *J Biol Chem* 1996; **271**: 5768–76

47 Goff JR, Burkey AR, Goff DJ, Jasmin L. Reorganization of the spinal dorsal horn in models of chronic pain: correlation with behaviour. *Neuroscience* 1998; **82**: 559–74

48 Gold MS. Spinal nerve ligation: What to blame for the pain and why. *Pain* 2000; **84**: 117–20

49 Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1992; **51**: 175–94

50 Guieu R, Peragut JC, Roussel P, *et al.* Adenosine and neuropathic pain. *Pain* 1996; **68**: 271–4

51 Hao JX, Blakeman KH, Yu W, Hultenby K, Xu XJ, Wiesenfeld-Hallin Z. Development of a mouse model of neuropathic pain following photochemically induced ischemia in the sciatic nerve. *Exp Neurol* 2000; **163**: 231–8

52 Herzberg U, Eliav E, Bennett GJ, Kopin IJ. The analgesic effects of R(+)-Win 55212'2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neurosci Lett* 1997; **221**: 157–60

53 Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Res* 1999; **822**: 17–25

54 Hohmann AG , Herkenham M. Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. *Neurosci Lett* 1998; **25**: 213–6

55 Holdcroft A, Hargreaves KM, Rice AS, *et al.* Cannabinoids and pain modulation in animals and humans. In: Devor M, Rowbotham RC, Wiesenfeld-Hallin Z, eds. *Progress in Pain Research and Management.* 2000; 915–26

56 Hua XY, Chen P, Yaksh TL. Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats. *Neurosci Lett* 1999; **276**: 99–102

57 Hwang JH, Yaksh TL. The effect of spinal GABA receptor agonists on tactile allodynia in a surgically-induced neuropathic pain model in the rat. *Pain* 1997; **70**: 15–22

58 Idanpaan-Heikkila JJ, Guilbaud G. Pharmacological studies on a rat model of trigeminal neuropathic pain: baclofen, but not carbamazepine, morphine or tricyclic antidepressants, attenuates the allodynia-like behaviour. *Pain* 1999; **79**: 281–90

59 Isaacson LG, Saffran BN, Crutcher KA. Nerve growth factor-induced sprouting of mature, uninjured sympathetic axons. *J Comp Neurol* 1992; **326**: 327–36

60 Jaggar SI, Habib S, Rice AS. The modulatory effects of bradykinin B1 and B2 receptor antagonists upon viscero-visceral hyper-reflexia in a rat model of visceral hyperalgesia. *Pain* 1998; **75**: 169–76

61 Janig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. *Prog Brain Res* 1996; **113**: 161–84

62 Jones MG, Munson JB, Thompson SW. A role for nerve growth factor in sympathetic sprouting in rat dorsal root ganglia. *Pain* 1999; **79**: 21–9

63 Kauppila T. Correlation between autotomy-behavior and current theories of neuropathic pain. *Neurosci Biobehav Rev* 1998; **23**: 111–29

64 Kawamata M, Omote K. Involvement of increased excitatory amino acids and intracellular Ca2+ concentration in the spinal dorsal horn in an animal model of neuropathic pain. *Pain* 1996; **68**: 85–96

65 Kim KJ, Yoon YW, Chung JM. Comparison of three rodent neuropathic pain models. *Exp Brain Res* 1997; **113**: 200–6

66 Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain* 1992; **50**: 355–63

67 Kim YI, Kim SH, Oh EJ, *et al.* Some membrane property changes following axotomy in A delta-type DRG cells are related to cold allodynia in rat. *Neuroreport* 1999; **10**: 1493–9

68 Kingery WS, Vallin JA. The development of chronic mechanical hyperalgesia, autotomy and collateral sprouting following sciatic nerve section in rat. *Pain* 1989; **38**: 321–32

69 Koerber HR, Mirnics K, Brown PB, Mendell LM. Central sprouting and functional plasticity of regenerated primary afferents. *J Neurosci* 1994; **14**: 3655–71

70 Kohama I, Ishikawa K, Kocsis JD. Synaptic reorganization in the substantia gelatinosa after peripheral nerve neuroma formation: aberrant innervation of lamina II neurons by Aβ afferents. *J Neurosci* 2000; **20**: 1538–49

71 Kovelowski CJ, Ossipov MH, Sun H, Lai J, Malan TP Jr, Porreca F. Supraspinal cholecystokinin may drive tonic descending facilitation mechanisms to maintain neuropathic pain in the rat. *Pain* 2000; **87**: 265–73

72 Kral MG, Xiong Z, Study RE. Alteration of Na+ currents in dorsal root ganglion neurons from rats with a painful neuropathy. *Pain* 1999; **81**: 15–24

73 Kupers R, Yu W, Persson JK, Xu X, Wiesenfeld-Hallin Z. Photochemically-induced ischemia of the rat sciatic nerve produces a dose-dependent and highly reproducible mechanical, heat and cold allodynia, and signs of spontaneous pain. *Pain* 1998; **76**: 45–59

74 Laird JM, Bennett GJ. An electrophysiological study of dorsal horn neurons in the spinal cord of rats with an experimental peripheral neuropathy. *J Neurophysiol* 1993; **69**: 2072–85

75 Lee BH, Won R, Baik EJ, Lee SH, Moon CH. An animal model of neuropathic pain employing injury to the sciatic nerve branches. *Neuroreport* 2000; **11**: 657–61

76 Lee BH, Yoon YW, Chung K, Chung JM. Comparison of sympathetic sprouting in sensory ganglia in three animal models of neuropathic pain. *Exp Brain Res* 1998; **120**: 432–8

77 Lekan HA, Carlton SM, Coggeshall RE. Sprouting of A beta fibers into lamina II of the rat dorsal horn in peripheral neuropathy. *Neurosci Lett* 1996; **208**: 147–50

78 Levine JD, Taiwao Y. Inflammatory pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 3rd edn. Edinburgh: Churchill Livingstone, 1994; 45–56

79 Li J, Simone DA, Larson AA. Windup leads to characteristics of central sensitization. *Pain* 1999; **79**: 75–82

80 Li Y, Dorsi MJ, Meyer RA, Belzberg AJ. Mechanical hyperalgesia after an L5 spinal nerve lesion in the rat is not dependent on input from injured nerve fibres. *Pain* 2000; **85**: 493–502

81 Liu CN, Amir R, Devor M. Effect of age and nerve injury on cross-excitation among sensory neurons in rat dorsal root ganglia. *Neurosci Lett* 1999; **259**: 95–8

82 Liu CN, Michaelis M, Amir R, Devor M. Spinal nerve injury enhances subthreshold membrane potential oscillations in DRG neurons: Relation to neuropathic pain. *J Neurophysiol* 2000; **84**: 205–15

83 Liu X, Eschenfelder S, Blenk KH, Janig W, Habler H. Spontaneous activity of axotomized afferent neurons after L5 spinal nerve injury in rats. *Pain* 2000; **84**: 309–18

84 Lyu YS, Park SK, Chung K, Chung JM. Low dose of tetrodotoxin reduces neuropathic pain behaviours in an animal model. *Brain Res* 2000; **871**: 98–103

85 Malcangio M, Tomlinson DR. A pharmacologic analysis of mechanical hyperalgesia in streptozotocin/diabetic rats. *Pain* 1998; **76**: 151–7

86 Malmberg AB, Basbaum AI. Partial sciatic nerve injury in the mouse as a model of neuropathic pain: behavioral and neuroanatomical correlates. *Pain* 1998; **76**: 215–22

87 Mannion RJ, Doubell TP, Coggeshall RE, Woolf CJ. Collateral sprouting of uninjured primary afferent A-fibres into the superficial dorsal horn of the adult rat spinal cord after topical capsaicin treatment to the sciatic nerve. *J Neurosci* 1996; **16**: 5189–95

88 Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK-801 and local nerve anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral mononeuropathy. *Brain Res* 1992; **576**: 254–62

89 Martini R. Animal models for inherited peripheral neuropathies: chances to find treatment strategies? *J Neurosci Res* 2000; **61**: 244–50

90 Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. *J Neurophysiol* 1994; **72**: 349–59

91 McLachlan EM, Janig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature* 1993; **363**: 543–6

92 McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68**: 217–27

93 Mendell LM. Physiological properties of unmyelinated fiber projection to the spinal cord. *Exp Neurol* 1966; **16**: 316–32

94 Merskey H, Bogduk N. *Classification of Chronic Pain*, 2nd edn. Seattle: IASP Press, 1994; 394

95 Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci USA* 1999; **96**: 7744–51

96 Mogil JS, Grisel JE. Transgenic studies of pain. *Pain* 1998; **77**: 107–28

97 Mogil JS, Wilson SG, Bon K, *et al.* Heritability of nociception II. 'Types' of nociception revealed by genetic correlation analysis. *Pain* 1999; **80**: 83–93

98 Neil A, Attal N, Guilbaud G. Effects of guanethidine on sensitization to natural stimuli and self-mutilating behaviour in rats with a peripheral neuropathy. *Brain Res* 1991; **565**: 237–46

99 Nordin M, Nystrom B, Wallin U, Hagbarth KE. Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. *Pain* 1984; **20**: 231–45

100 OmanaZapata I, Khabbaz MA, Hunter JC, Clarke DE, Bley KR. Tetrodotoxin inhibits neuropathic ectopic activity in neuromas, dorsal root ganglia and dorsal horn neurons. *Pain* 1997; **72**: 41–49

101 Pan HL, Eisenach JC, Chen SR. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. *J Pharmacol Exp Ther* 1999; **288**: 1026–30

102 Perl ER, Willis WD, eds. Alterations in responsiveness of cutaneous nociceptors: sensitization by noxious stimuli and the induction of adrenergic responsiveness by nerve injury. *Hyperalgesia and Allodynia*. New York: Raven Press, 1992; 59–79

103 Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997; **74**: 129–80

104 Petersen M, Eckert AS, Segond von Banchet G, Heppelmann B, Klusch A, Kniffki KD. Plasticity in the expression of bradykinin binding sites in sensory neurons after mechanical nerve injury. *Neuroscience* 1998; **83**: 949–59

105 Porreca F, Tang QB, Bian D, Riedl M, Elde R, Lai J. Spinal opioid mu receptor expression in lumbar spinal cord of rats following nerve injury. *Brain Res* 1998; **795**: 197–203

106 Quartaroli M, Carignani C, Dal Forno G, *et al.* Potent antihyperalgesic activity without tolerance produced by glycine site antagonist of *N*-methyl-D-aspartate receptor GV196771A. *J Pharmacol Exp Ther* 1999; **290**: 158–69

107 Rabben T, Skjelbred P, Oye I. Prolonged analgesic effect of ketamine, an N-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. *J Pharmacol Exp Ther* 1999; **289**: 1060–6

108 Ramer MS, Bisby MA. Rapid sprouting of sympathetic axons in dorsal root ganglia of rats with a chronic constriction injury. *Pain* 1997; **70**: 237–44

109 Ramer MS, Thompson SW, McMahon SB. Causes and consequences of sympathetic basket formation in dorsal root ganglia. *Pain* 1999; **6** (Suppl.): S111–20

110 Rice ASC, Casale R. Microneurography and the investigation of pain mechanisms. *Pain Rev* 1994; **1**: 121–37

111 Ro L, Chen S, Tang L, Chang H. Local application of anti-NGF blocks the collateral sprouting in rats following chronic constriction injury of the sciatic nerve. *Neurosci Lett* 1996; **218**: 87–90

112 Rowbotham MC. Kalso E, McQuay HJ, Wiesenfeld-Hallin Z, eds. The debate over opioids and neuropathic pain. *Opioid Sensitivity of Chronic Non-cancer Pain*. Seattle: IASP Press, 1999; **18**: 307–17

113 Rowbotham MC, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for treatment of postherpetic neuralgia. *JAMA* 1998; **280**: 1837–43

114 Santicioli P, Del Bianco E, Tramontana M, Maggi CA. Adenosine inhibits action potential-dependent release of calcitonin gene-related peptide- and substance P-like immunoreactivities from primary afferents in rat spinal cord. *Neurosci Lett* 1992; **144**: 211–4

115 Sebert ME, Shooter EM. Expression of mRNA for neurotrophic factors and their receptors in the rat dorsal root ganglion and sciatic nerve following nerve injury. *J Neurosci Res* 1993; **36**: 357–67

116 Seltzer Z, Dubner R, and Shir Y. A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain* 1990; **43**: 205–18

117 Sheen K, Chung JM. Signs of neuropathic pain depend on signals from injured nerve fibers in a rat model. *Brain Res* 1993; **610**: 62–8

118 Shir Y, Seltzer Z. Effects of sympathectomy in a model of causalgiform pain produced by partial sciatic nerve injury in rats. *Pain* 1991; **45**: 309–20

119 Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; **83**: 389–400

120 Sivilotti L, Woolf CJ. The contribution of GABAA and glycine receptors to central sensitization: disinhibition and touch-evoked allodynia in the spinal cord. *J Neurophysiol* 1994; **72**: 169–79

121 Smith GD, Harrison SM, Birch PJ, Elliott PJ, Malcangio M, Bowery NG. Increased sensitivity to the antinociceptive activity of (+/–)-baclofen in an animal model of chronic neuropathic, but not chronic inflammatory hyperalgesia. *Neuropharmacology* 1994; **33**: 1103–8

122 Sollevi A, Belfrage M, Lundeberg T, Segerdahl M, Hansson P. Systemic adenosine infusion: a new treatment modality to alleviate neuropathic pain. *Pain* 1995; **61**: 155–8

123 Sotgiu ML, Biella G. Differential effects of MK-801, a N-methyl-D-aspartate non-competitive antagonist, on the dorsal horn neuron hyperactivity and hyperexcitability in neuropathic rats. *Neurosci Lett* 2000; **283**: 153–6

124 Stanfa LC, Dickenson AH, Xu X, Wiesenfeld-Hallin Z. Cholecystokinin and morphine analgesia: variations on a theme. *Trend Pharmacol Sci* 1994; **15**: 65–6

125 Stein C, Schafer M, Cabot PJ, *et al.* Peripheral opioid analgesia. *Pain Rev* 1997; **4**: 173–87

126 Stiller CO, Cui JG, O'Connor WT, Brodin E, Meyerson BA, Linderoth B. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. *Neurosurgery* 1996; **39**: 367–74

127 Suzuki R, Chapman V, Dickenson AH. The effectiveness of spinal and systemic morphine on rat dorsal horn neuronal responses in the spinal nerve ligation model of neuropathic pain. *Pain* 1999; **80**: 215–28

128 Takasaki I, Andoh T, Shiraki K, Kuraishi Y. Allodynia, and hyperalgesia induced by herpes simplex virus type-1 infection in mice. *Pain* 2000; **86**: 95–101

129 Tandrup T, Woolf CJ, Coggeshall RE. Delayed loss of small dorsal root ganglion cells after transection of the rat sciatic nerve. *J Comp Neurol* 2000; **422**: 172–80

130 Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, Dooley DJ, Boden P, Singh L. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res* 1998; **29**: 233–49

131 Thompson SW, Bennett DL, Kerr BJ, Bradbury EJ, McMahon SB. Brain-derived neurotrophic factor is an endogenous modulator of nociceptive responses in the spinal cord. *Proc Natl Acad Sci USA* 1999; **96**: 7714–8

132 Thompson SW, Majithia AA. Leukemia inhibitory factor induces sympathetic sprouting in intact dorsal root ganglia in the adult rat in vivo. *J Physiol* 1998; **506**: 809–16

133 Tong YG, Wang HF, Ju G, Grant G, Hokfelt T, Zhang X. Increased uptake and transport of cholera toxin B-subunit in dorsal root ganglion neurons after peripheral axotomy: possible implications for sensory sprouting. *J Comp Neurol* 1999; **404**: 143–58

134 Utzschneider D, Kocsis J, Devor M. Mutual excitation among dorsal root ganglion neurons in the rat. *Neurosci Lett* 1992; **146**: 53–6

135 Wagner R, Janjigian M, Myers RR. Anti-inflammatory interleukin-10 therapy in CCI neuropathy decreases thermal hyperalgesia, macrophage recruitment, and endoneurial TNF-alpha expression. *Pain* 1998; **74**: 35–42

136 Wall PD. Neuropathic pain and injured nerve: central mechanisms. *Br Med Bull* 1991; **47**: 631–43

137 Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve ligated rats. *Pain* 1983; **17**: 321–39

138 Wall PD, Devor M, Inbal FR, *et al.* Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa. *Pain* 1979; **7**: 103–11

139 Wall PD, Gutnick M. Ongoing activity in peripheral nerves: The physiology and pharmacology of impulses originating from a neuroma. *Exp Neurol* 1974; **43**: 580–93

140 Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section. *Neuroscience* 1986; **17**: 1199–1205

141 Waxman SG, Dib Hajj S, Cummins TR, Black JA. Sodium channels and pain. *Proc Natl Acad Sci USA* 1999; **96**: 7635–9

142 Waxman SG, Kocsis JD, Black JA. Type III sodium channel mRNA is expressed in embryonic but not adult spinal sensory neurons, and is reexpressed following axotomy. *J Neurophysiol* 1994; **72**: 466–70

143 White DM, Cousins MJ. Effect of subcutaneous administration of calcium channel blockers on nerve injury-induced hyperalgesia. *Brain Res* 1998; **801**: 50–8

144 Woolf CJ. Windup and central sensitization are not equivalent. *Pain* 1996; **66**: 105–8

145 Woolf CJ and Mannion RJ. Pain: neuropathic pain: aetiology, symptoms, mechanisms and managment. *Lancet* 1999; **353**: 1959–64

146 Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992; **355**: 75–8

147 Woolf CJ, Shortland P, Reynolds M, Ridings J, Doubell T, Coggeshall RE. Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy. *J Comp Neurol* 1995; **360**: 121–34

148 Wu CL, Marsh A, Dworkin RH. The role of sympathetic nerve blocks in herpes zoster and postherpetic neuralgia. *Pain* 2000; **87**: 121–9

149 Xiao WH, Bennett GJ. Synthetic omega-conopeptides applied to the site of nerve injury suppress neuropathic pains in rats. *J Pharmacol Exp Ther* 1995; **274**: 666–72

150 Xu X, Hao J, Aldskogius H, Seiger A, Wiesenfeld-Hallin Z. Chronic pain-related syndrome in rats after ischemic spinal cord lesion: a possible animal model for pain in patients with spinal cord injury. *Pain* 1992; **48**: 279–90

151 Xu X, Puke MJ, Verge VM, Wiesenfeld-Hallin Z, Hughes J, Hokfelt T. Up-regulation of cholecystokinin in primary sensory neurons is associated with morphine insensitivity in experimental neuropathic pain in the rat. *Neurosci Lett* 1993; **152**: 129–32

152 Yaksh TL. Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain* 1989; **37**: 111–23

153 Yiangou Y, Birch R, Sangameswaran L, Eglen R, Anand P. SNS/PN3 and SNS2/NaN sodium channel-like immunoreactivity in human adult and neonate injured sensory nerves. *FEBS Lett* 2000; **467**: 249–52

154 Yoon YW, Na HS, Chung JM. Contributions of injured and intact afferents to neuropathic pain in an experimental rat model. *Pain* 1996; **64**: 27–36

155 Zhang X, Bao L, Shi TJ, Ju G, Elde R, Hokfelt T. Down-regulation of mu-opioid receptors in rat and monkey dorsal root ganglion neurons and spinal cord after peripheral axotomy. *Neuroscience* 1998; **82**: 223–40

Note added in proof

Since the original submission of this article, an important study has appeared.[1] This demonstrates that, following peripheral nerve injury, an increased expression of the noxious heat gated VR-1 receptor, which in the physiological state is generally restricted to C-fibre cell bodies, is observed on the DRG cell bodies of uninjured A-fibres. This supports the hypothesis that uninjured neurones contribute to the development and maintenance of neuropathic pain states and that the phenotype of primary afferent neurones which express VR-1 is altered.

1 Hudson LJ, Bevan SJ, Wotherspoon G, Gentry GC, Fox A, Winter J. VR-1 protein expression increases in undamaged DRG neurons after partial nerve injury. *Eur J Neurosci* (in press).

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Developments in local anaesthetic drugs

J. B. Whiteside* and J. A. W. Wildsmith

University Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
**Corresponding author*

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Most of the recent developments in local anaesthetics have been a direct consequence of the recognition, 20 yr ago, of the acute, life-threatening cardiotoxicity of bupivacaine.[5] All local anaesthetics produce a dose dependent delay in the transmission of impulses through the cardiac conduction system by their action on the cardiac sodium and potassium channels. However, overt cardiotoxicity usually only becomes apparent as the last feature of a reasonably predictable sequence of changes.[33] One of the specific features of bupivacaine is that clinical evidence of accumulation of the drug in plasma may be diminished until a fairly late stage because of its high affinity for plasma protein binding sites. The 'free' concentration of drug in plasma remains low until all the protein binding sites are fully occupied after which it increases rapidly, and toxicity can occur without patients exhibiting signs of CNS toxicity before cardiovascular collapse.[49 110] In addition to, and probably more important than, this pharmacokinetic component to its toxicity, bupivacaine has been shown to have selective cardiac effects related to the slow rate at which it dissociates from the sodium channel.[29] An important aspect of this toxicity is that it involves a significant degree of stereo-specificity, with the 'S' isomer showing significantly less cardio-depressant effect than the 'R'.[99]

These findings generated two parallel areas of research, one clinical and the other laboratory; the outcome of both has affected clinical practice. The clinical programme was aimed at avoidance of the rapid accidental intravascular injection of a large dose of bupivacaine, the common factor in all serious reactions. Much study of 'test' doses has shown that no such test is completely reliable at identifying accidental intravascular placement. Thus, it is still essential that the main dose of local anaesthetic is injected incrementally (4–5 ml at a time) with sufficient pause between each bolus to allow identification of any systemic consequences. The laboratory research programme was aimed at identifying a local anaesthetic with a similar clinical profile, but with less cardiotoxicity than bupivacaine. Given that a more cautious approach to clinical use seems to have prevented any further deaths, it may be argued that the expense of a new agent is unnecessary. However, it is an agent with a relatively low therapeutic index, and as little as 50 mg has caused primary ventricular fibrillation on accidental i.v. administration in a susceptible patient. Less risk of toxicity may be justification alone for new drugs when very large doses are required as in brachial plexus block. However, perhaps a new drug should offer additional advantages when used in other ways if the expense is to be justified.

The search for alternatives to bupivacaine has concentrated on amide-linked agents, which in current practice have largely superseded the ester type drugs. Investigation of the possible aetiological mechanisms of local anaesthetic induced cardiotoxicity, along with advances in stereoselective synthesis, have demonstrated the potential clinical advantages of agents comprised of a single enantiomer.[1 97 99] Of the commonly used, older amide drugs, only lidocaine is not 'chiral'; for example, it exists as a single structural entity at molecular level. Prilocaine, mepivacaine, and bupivacaine all have an 'asymmetric' carbon atom which means that traditional manufacturing methods result in the production of equal amounts of 'S' and 'R' isomers, something which is reflected in the clinically available preparations. Ropivacaine and levobupivacaine are two relatively new amide local anaesthetic agents that have been produced in order to address the issue of bupivacaine cardiotoxicity. Each is produced as a pure 'S' isomer. Levobupivacaine is the 'S' isomer of bupivacaine. Ropivacaine is the propyl analogue of, bupivacaine having a butyl group in the same position.

Current developments are not exclusively restricted to variations on the traditional amide drug theme as a response to rare toxic reactions. Other work is looking to identify

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agents that interrupt nerve transmission in a more specific way with the aim of maximizing analgesia and minimizing other manifestations of nerve block. Much of this research is concentrating on the modulation of synaptic transmission at spinal cord level and is beyond the scope of this review. However, manipulation of the effects of the physico-chemical properties of local anaesthetic drugs can influence the degree of differential nerve block,[20 103] and the lower lipid solubility of ropivacaine results in less motor block than bupivacaine. Studies of an agent with very significantly lower lipid solubility than these (butyl amino-benzoate[68 91 92]) may yet provide the practising anaesthetist with a 'local analgesic' not only with a specific action, but one with a duration measured in weeks. The prolongation of effect is due more to the formulation, a suspension, than to the drug itself. An alternative 'slow release' strategy is the incorporation of standard drugs into liposomes,[16 38 53 71] but this review will concentrate on drugs. Problems with the liposome method have been reported.[39]

The clinical use of the new drugs mentioned above will be the prime focus of this review, but the obvious importance of chirality to the pharmacology of ropivacaine and levobupivacaine means that some explanation is appropriate. Butyl amino-benzoate represents an extreme example of the differential nerve blocking effect of local anaesthetics, as well as an indication of how slow release preparations may be used to prolong their action. Finally, there will be some consideration of articaine. This is not a new drug and, unlike the others mentioned above, it has a relatively short duration, but there has been some renewed interest in it. This interest may be increased by the recent withdrawal of a large number of prilocaine preparations because articaine has similar properties.[17]

Chirality and local anaesthetics

Chirality is a word derived from the Greek chiros meaning 'handed'. Chemically, a chiral compound is one that contains at least one tetraco-ordinate carbon (or sulphur) atom to which four different atoms or chemical groups are attached. If a molecule contains one such 'asymmetric' carbon atom, two distinct spatial arrangements are possible, each a mirror image of the other. These 'stereo-isomers' are molecules with identical atomic composition and chemical properties, but the different spatial arrangement of their atoms means that they do not match when superimposed one upon the other. A pair of such stereo-isomers are called enantiomers, and each rotates plane-polarized light in equal magnitude, but in opposite directions. When a compound contains equimolar amounts of the two enantiomers it is referred to as a 'racemate' or 'racemic' mixture. Enantiomers have identical physico-chemical properties, so they will have the same pKa and lipid solubility figures.[95] However, they differ, both qualitatively and quantitatively, in regard to pharmacokinetic and pharmacodynamic properties, because of stereoselective interactions (i.e., those as a result of differences in three-dimensional structure) at molecular sites of drug action.

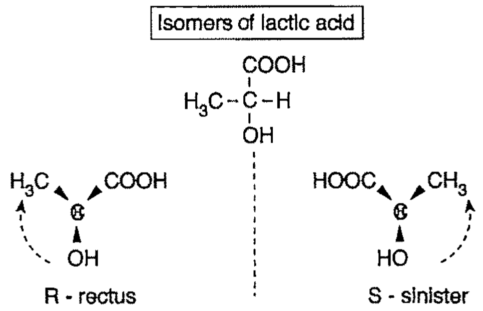

Fig 1 Structural chemistry of the isomers of lactic acid. The top representation shows the standard two-dimensional representation. In the other two, the smallest group (-H) attached to the central carbon atom is 'directed' away from the viewer. If the sequence of the other three (smallest to largest) is 'clockwise' as viewed, it is an R isomer, and an S isomer if the sequence is reversed.

Each stereo-isomer of any pair may be described in a number of ways, but the current standard is the 'Sequence Rule Notation'.[25] This is based on attaching an order of priority to substituent groups (or atoms) attached to the central chiral atom, having identified the 'smallest' of the four first. The molecule is 'positioned' with this smallest group directed away from the 'viewer' and note taken of the sizes of the other three. If the sequence from smallest to largest is 'clockwise', it is defined as a 'R' isomer from the Latin rectus (right), whereas if the sequence is 'anticlockwise' the isomer is defined as 'S' from the Latin sinister (left). These are known as absolute descriptors and may be most simply illustrated by reference to the isomers of lactic acid (Fig. 1).

However, the best-known method of referring to the chirality of a molecule relates to the effect it has on the rotation of plane polarized light, either clockwise (+) or anticlockwise (–)—the relative descriptors. Unfortunately, there is no consistency between the absolute and relative descriptors. Within an homologous series of compounds the S/R notation may change as the length of a particular side chain increases so the full description of a chiral compound may be given by a combination of both descriptors (e.g. S(–) bupivacaine).

Differences in both the pharmacokinetic and pharmacodynamic properties of the different isomers of various local anaesthetic drugs have been recognized for many years. Prilocaine was probably the first agent to be studied extensively,[2] but the costs of production were then prohibitive for clinical availability and the differences between the isomers were of relatively little clinical impact. The local anaesthetic and toxic effects of the enantiomers of bupivacaine were first described in 1972 by Aberg and colleagues,[1] who showed that the S(–) enantiomer is less toxic than the R(+) form. Subsequent studies confirmed the lower neurotoxicity and cardiotoxicity of the S(–) enantiomer in animal models.[60 72 99] Human studies have also

Table 1 Physico-chemical properties and plasma protein binding characteristics of local anaesthetic agents.[95 104] PK$_a$=dissociation constant

Drug	PKa	Partition coefficient	Percentage protein bound
Lidocaine	7.8	43	64
Prilocaine	7.8	25	55
Mepivacaine	7.8	21	77
Bupivacaine	8.2	346	95.5
Levobupivacaine	8.2	346	93.4
Ropivacaine	8.2	115	94

shown that larger doses of S(–) bupivacaine than racemic bupivacaine are required before the onset of neurological symptoms.[12]

Ropivacaine is the 'S' isomer of the propyl analogue of mepivacaine and bupivacaine. The parent compound of ropivacaine was, like the other two, first synthesized in the 1950s,[4] but they were selected for further development as short and long-acting agents, respectively. It was only when concerns about the cardiotoxicity of bupivacaine became apparent that ropivacaine was evaluated fully. The S(–) enantiomer was selected initially because it has a longer duration of action than the R(+),[3] but later animal studies showed that ropivacaine dissociates from sodium channels more rapidly, produces less accumulation of sodium channel block and is less cardiotoxic than racemic bupivacaine.[7 78 85] Infusion studies in human volunteers have confirmed that larger doses are required to produce early features of neurotoxicity and cardiotoxicity than racemic bupivacaine.[65 88] The commercial preparation has an enantiomeric purity of 99.5%.[44]

Ropivacaine

Ropivacaine (*N-n*-propyl 2′,6′-pipecoloxylidide) is an amino-amide local anaesthetic, some important basic aspects of which have been described already. It was first registered for clinical use in 1996 and a full review of its clinical pharmacology was published at that time.[73] As well as having less cardiotoxicity, there is evidence that any such effect occurring after inadvertent intravascular injection may be more easily reversed than is the case with bupivacaine.[9 45 83]

The physico-chemical properties of ropivacaine (Table 1) suggest that its rate of onset (related to pKa) should be similar to that of bupivacaine, and that its absolute potency (lipid solubility) and duration of effect (protein binding) should be slightly less.

In addition, the lower lipid solubility of ropivacaine would predict that it is likely to produce a greater differential block of sensory and motor function than bupivacaine. Laboratory studies have confirmed these predictions,[10 86 103] but selection of the longer acting S(–) isomer should compensate for the possible shorter duration. Thus, ropivacaine has other potential advantages besides that of reduced cardiotoxicity.

Further evaluation in both animal and volunteer human studies confirmed that ropivacaine is an effective local anaesthetic and showed that, unlike bupivacaine, it has a slight vasoconstrictor effect at lower concentrations.[28 36 66] Epinephrine was found to have little effect on the local action or the resultant systemic concentrations of ropivacaine in human studies.[28 56 81]

Clinical efficacy

Ropivacaine has been compared with bupivacaine in many clinical trials involving most forms of regional anaesthesia. Most studies have shown that the onset, potency and duration are very similar to those of bupivacaine. However, some studies, particularly those utilizing the concept of Minimum Local Analgesic Concentration (MLAC) in epidural analgesia, have questioned whether the difference in cardiotoxicity seen between the two agents is in fact a result of an absolute difference in potency.[27 84] The suggestion is that the therapeutic ratio of the two may be the same. Such concerns must be viewed against the important basic principle that the local, and subsequent systemic, dynamics of a particular local anaesthetic will depend on the site of injection.[8] Thus, each clinical application must be considered in turn.

Wound infiltration

Ropivacaine has been used successfully for post-operative analgesia in patients undergoing inguinal herniorrhaphy[80] and open cholecystectomy.[61] Equal doses (100 mg) of ropivacaine and bupivacaine have been shown to provide similar analgesia after inguinal hernia surgery.[41] The intrinsic vasoconstrictive properties of ropivacaine may help explain the findings of one study which demonstrated cutaneous anaesthesia two to three times longer than that produced by bupivacaine.[28] Some authors have questioned the safety of this because of the possibility of inducing microcirculatory insufficiency or compromising end-arterial blood supply.[94] There has been one report of local ischaemia after the use of 0.75% ropivacaine for penile block, but no long-term sequelae were observed.[21] Therefore, ropivacaine may be unsuitable for infiltration in tissues without collateral blood supply.

Major nerve block

A large number of studies on the use of ropivacaine for brachial plexus anaesthesia, utilizing a variety of techniques, have been published.[43 57] The majority of studies suggest that the clinical outcome is similar to that of equivalent doses of bupivacaine,[58 59 96] with the 0.25% concentration of both drugs being associated with an unacceptable incidence of inadequate block of either sensory or motor nerves. Some, more recent studies have shown a significantly faster onset in both upper and lower limb blocks with ropivacaine than with an equal dose of

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bupivacaine.[15 43] Bertini and colleagues also demonstrated a better quality of block with ropivacaine as indicated by intra-operative opioid requirements and patient satisfaction scores.[15]

Although there is some variation between the reports in the literature, an overview suggests that there may be no more than slight differences in onset, but no difference between ropivacaine and bupivacaine in completeness or duration of block. Both drugs produce effective long-acting local anaesthesia.

Spinal anaesthesia

Ropivacaine has been used relatively infrequently for spinal anaesthesia. Its very early evaluation included two studies of the intrathecal injection of glucose-free solutions performed primarily for safety reasons to confirm that accidental intrathecal injection during epidural block would be without adverse sequelae.[98 100] Sensory block of variable extent and intermediate duration was produced. Currently, ropivacaine is not licensed for intrathecal use, but two more recent, clinical studies have compared ropivacaine unfavourably with bupivacaine.[51 77]

Gautier and colleagues[51] used glucose-free preparations, but in larger volumes of less concentrated solutions than are normally used in clinical practice. The onset and extent of sensory block were similar, but both the duration of that sensory block and the degree of motor block produced were less with ropivacaine. These findings, particularly the shorter duration of action, led the authors to claim that ropivacaine is less potent than bupivacaine and that it offers no significant advantage. However, it is noteworthy that the patients who received ropivacaine passed urine and mobilized more rapidly than those who received bupivacaine.

McDonald and colleagues[77] compared hyperbaric preparations of the two drugs in volunteers not undergoing surgery. The concentrations of their solutions were also less than are normally used clinically, as were the total doses injected. The two drugs produced sensory blocks of similar onset and extent, but there was less motor block, which regressed faster, with ropivacaine. Again, on the basis of the shorter duration of action and despite equivalence in the onset and extent of sensory block, the conclusion was that ropivacaine is less potent than bupivacaine. This study also noted a higher incidence of backache after ropivacaine and concluded that the incidence of side effects was higher, even though the difference was not statistically significant.

However, more recent work has shown that glucose containing solutions of ropivacaine in concentrations and doses more appropriate to spinal anaesthesia produce a clinical block profile that is very appropriate to much of the surgery for which this application of regional anaesthesia is currently used.[102] No direct comparison of ropivacaine and bupivacaine in formulations more suited to clinical use is yet available, but ropivacaine does seem worthy of more definitive study for spinal anaesthesia. There is also some need for questioning the interpretation of a difference in duration as an indicator of a difference in potency.[105]

Epidural anaesthesia and analgesia

The historical background, the potential for less cardiotoxicity, and the early evidence suggesting that the motor block produced by ropivacaine is less intense and of shorter duration than with bupivacaine, have all led to extensive evaluation of its role in epidural block.[18–19 47 63 107–108 111–112] These are ideal qualities for an agent for epidural use, where accidental i.v. injection of large doses of local anaesthetic is a potential hazard and where preservation of lower limb motor function is often desirable.

Early, 'open' studies of ropivacaine showed that it could be used to provide long-acting, good quality anaesthesia for surgery when administered by the lumbar route.[31 101] The lower lipid solubility of ropivacaine, and the *in vitro* and *in vivo* demonstration of slightly lower potency than bupivacaine,[46 86] led some investigators to compare ropivacaine with somewhat lower concentrations of bupivacaine.[62 107–108] They demonstrated similar onset and extent of both motor and sensory block, and similar duration of motor block, but slightly longer duration of analgesia with the more concentrated solutions of ropivacaine. However, when direct comparison of equal concentrations have been made, in both the obstetric and non-obstetric population, no significant differences in onset, speed or duration of sensory block were found, but the motor block was less intense and of shorter duration.[18 54 79]

This work was for 'anaesthetic' use in a wide range of clinical settings, but most of the studies of ropivacaine as an 'analgesic' have been performed in the obstetric population. Maternal safety, good patient mobility during labour and minimal need for obstetric intervention are key outcomes in this field of practice and the lower cardiotoxic potential and the greater degree of sensory and motor block separation have led some to suggest that ropivacaine offers significant advantages over bupivacaine.[74]

Many studies have compared the two during labour, all of them demonstrating similar degrees of pain relief with equal doses of the agents.[14 40 50 75–76 82] A meta-analysis of such studies showed that ropivacaine was associated with significantly more spontaneous vaginal deliveries, fewer instrumental deliveries and better neonatal outcome scores than bupivacaine.[109] Both agents have also been shown to be equally effective when combined in low doses with opioids.[26 52 89]

However, more recent studies have questioned the relative potencies of ropivacaine and bupivacaine.[27 84] Using an 'up–down' sequential allocation method to compare the minimum local analgesic concentration (MLAC) of these agents it has been suggested that ropivacaine may be 40% less potent than bupivacaine. This method, first described by Columb and Lyons in 1995,[30] aims to determine the 'ED_{50}', or more correctly the effective concentration of each agent for 50% of patients, using a fixed volume of local anaesthetic. The results have been used to support an argument that any advantages that ropivacaine may have over bupivacaine in terms of reduced motor block and risk of cardiotoxicity must be balanced against the apparent reduction in potency. The implication is that more drug will be required and any potential advantage lost.

Against this conclusion, a number of authorities have questioned the basic validity of the MLAC method for determining local anaesthetic potency.[37 93] First, the clinical relevance of the figure obtained has been questioned, because only 50% of patients studied receive obtain pain relief. Second, while the results are expressed as a concentration, it is inherent in the method that the dose of drug injected changes as well as the concentration. Third, analyses based on the results of the MLAC method make assumptions about the shape of the remainder of the 'dose' response curve even though only one point on it has been obtained. Without formal studies to define the dose response curves for both ropivacaine and bupivacaine it is impossible to speculate on the shape of the curves based on a single data point. Thus, the findings of the two MLAC studies comparing ropivacaine and bupivacaine must be questioned because they contradict directly the results of other clinical studies in which pain relief has been provided for all the patients. These, as has already been noted, have shown equal degrees of pain relief with equal concentrations of the two agents, but with significant other advantages for ropivacaine.

Levobupivacaine

At the time that ropivacaine was being developed, it was not fully appreciated that the cardiotoxicity of bupivacaine exhibits a significant degree of enantioselectivity.[1 69] However, once this was recognized, the S(–) enantiomer (levobupivacaine) was developed as an alternative long-acting local anaesthetic. Human volunteer studies have demonstrated that S(–) bupivacaine is better tolerated than racemic bupivacaine,[12] although it produces a greater prolongation of the QRS complex than ropivacaine in conscious rats.[42] The pharmacology of levobupivacaine has been reviewed extensively elsewhere.[48]

Levobupivacaine has only been introduced into clinical practice recently and, as a consequence, experience of its use is more limited than with ropivacaine. One important point that must be noted by clinicians using the commercial preparation is that there has been a change in the regulations governing the way in which drug salts are presented and labelled in Europe. As a new drug, levobupivacaine comes under the aegis of Directive 91/507 of the European Union Part 2, section A. Clause 3.3 of this directive states that formulations of a drug which exists as a hydrate or salt (both apply to most local anaesthetics) must be expressed in terms of the milligram concentration of the active moiety. Thus, a solution of levobupivacaine 0.5% contains 5 mg ml^{-1} of the base drug. However, both ropivacaine and racemic bupivacaine predate this directive so 0.5% solutions of these drugs contain 5 mg ml^{-1} of the hydrochloride salt. Thus, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of racemic bupivacaine of the same concentration.[70]

Clinical efficacy

As with ropivacaine, most of the studies of levobupivacaine have used racemic bupivacaine as the comparator agent. Given that isomers have identical physico-chemical properties, it would be expected that the clinical performances of the two would be identical. As is the case with ropivacaine, the S(–) isomer of bupivacaine produces more vasoconstriction than the R(+) isomer.[6 22] In theory, this might be detrimental in some vascular beds (e.g. by decreasing uterine blood flow), but no adverse effects on uterine blood flow were seen in animal models after the administration of levobupivacaine.[87]

Wound infiltration

Two studies have demonstrated similar effects on pain relief, supplementary analgesic requirements and patient satisfaction when 0.25% levobupivacaine and 0.25% bupivacaine were used for analgesia after inguinal hernia repair.[13 64]

Major nerve block

A double-blind comparison of equal doses of levobupivacaine and bupivacaine for supraclavicular brachial plexus block[34] found almost no difference in clinical block profile. There was a slightly longer duration of sensory block with levobupivacaine, but the difference was not statistical significant.

Spinal anaesthesia

One open, non-comparative study of the clinical effects of a plain solution of levobupivacaine in spinal anaesthesia for lower limb surgery has been published.[23] Variable spread of block, which was occasionally unsatisfactory for surgery, was found. As with bupivacaine, this can be attributed largely to the hypobaric nature of the solution at 37°C.

Epidural block

In the non-obstetric population, two studies have compared levobupivacaine with bupivacaine in epidural block. Comparable degrees of sensory and motor block were produced with 15 ml of 0.5% solution of either drug in patients undergoing lower limb surgery.[35] There were no differences in the quality of surgical anaesthesia and similar findings were reported when the two drugs were compared for lower abdominal surgery.[67]

In the obstetric population, the two drugs have been compared in 0.5% solutions during epidural anaesthesia for Caesarian section.[11] There were no differences in block characteristics, quality of anaesthesia or neonatal outcome.

In addition, there have been two comparisons of their use for epidural analgesia during labour.[24 32] The analgesia produced by the drugs was broadly similar, but significantly more patients in the levobupivacaine group required a second injection to achieve pain relief in one of the studies.[24] However, this appears to have been related to the inclusion in that group of patients with a greater degree of cervical dilation and a higher proportion of those in whom labour had been induced in the levobupivacaine group.

Ropivacaine and levobupivacaine

An overview of the relatively small amount of published information on the clinical use of levobupivacaine seems to be that its clinical effects are, as might be expected, identical to those of bupivacaine. Thus, its only potential advantage is a potential safety one when large doses are required. There are, as yet, no definitive published comparisons with ropivacaine, and certainly no clinical ones, although it seems reasonable to conclude that ropivacaine differs from levobupivacaine in the same ways as bupivacaine. Some basic science work suggests that the risk of clinical toxicity is less with ropivacaine, but the key to safe practice must remain the avoidance of accidental intravascular injection. Time will tell whether either drug will displace bupivacaine as the standard long-acting local anaesthetic.

Other developments

Butyl amino-benzoate

Butyl amino-benzoate (BAB) is an amino ester first discovered in 1923. Initially, it was thought unsuitable for anaesthetic use because of its extremely low pK_a, low water solubility, poor dural permeability, and rapid hydrolysis. However, over 60 yr after it was first discovered, suspension preparations in polyethylene glycol and polysorbate-80 (Butamben) were manufactured which produced long-lasting analgesia when given epidurally to cancer patients as an alternative to alcohol or phenol neurolysis.[68 91] More recently, BAB has also been used successfully in the treatment of both cancer and non-cancer pain.[92]

One attribute claimed for this preparation is an apparent selectivity of effect on Aδ- and C-fibres, so that it produces minimal motor block with sparing of bladder and bowel function.[68 92] Attempts to formulate other agents, such as lidocaine, in a similar suspension preparation were associated with more neuropathological changes and a much shorter duration of action.[39] It seems likely that the low lipid solubility of BAB means that it is unable to diffuse through the myelin sheaths of other types of nerve fibre, with the long duration of effect being to the 'slow release' properties of the suspension. Further study of a drug with a very interesting clinical profile is warranted.

Articaine

Although not as old as BAB, this is also not a new agent. It has been used widely in dental practice in Canada and parts of Europe for many years, but is not being introduced into other countries. It is an anilide local anaesthetic agent, differing from the standard amide agents such as lidocaine by having a thiophene instead of a benzene ring within its structure.[106] Initially, dental practitioners felt that it had a faster onset and wider spread than other agents, and this prompted further evaluation. However, double-blind comparisons with prilocaine and lidocaine in infiltration, IVRA and epidural blocks failed to demonstrate any significant differences.[17 55 90] It is, therefore, unlikely that a place will be found for this agent within current anaesthetic practice although the recent reduction in availability of prilocaine might change this because it has similarly low potential for systemic toxicity.

Declaration of interest

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References

1 Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmacol Toxicol* 1972; **31**: 444–50

2 Åckerman B, Persson H, Tegner C. Local anaesthetic properties of the optically active isomers of prilocaine (Citanest®) *Acta Pharmacol Toxicol* 1967; **25**: 233–41

3 Åckerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiol Scand* 1988; **32**: 571–8

4 Af Ekenstam B, Egner B, Petersson G. Local anaesthetics: 1. *N*-alkyl pyrrolidine and *N*-alkyl piperidine carboxylic amides. *Acta Chem Scand* 1957; **11**: 1183–1190

5 Albright GA. Cardiac arrest following regional anaesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51**: 285–7

6 Aps C, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. *Br J Clin Pharmacol* 1978; **6**: 63–8

7 Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V_{max}). *Pharmacol Toxocol* 1988; **63**: 96–104

8 Arthur GR, Wildsmith JAW, Tucker GT. Pharmacology of local anaesthetic drugs. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia.* London: Churchill Livingstone, 1993; 29–45

9 Arthur GR, Covino BG. What's new in local anesthetics? *Anesth Clin North Am* 1988; **6**: 357–70

10 Bader AM, Datta S, Flanagan H, Covino BG. Comparison of bupivacaine and ropivacaine induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg* 1989; **68**: 724–7

11 Bader AM, Tsen LC, Camaan WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for caesarean delivery. *Anesthesiology* 1999; **90**: 1596–601

12 Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine

and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharm* 1998; **46**: 245–9

13 Bay-Nielsen M, Klarskov B, Bech K, Andersen J, Kehlet H. Levobupivacaine *vs* bupivacaine as infiltration anaesthesia in ingunal herniorrhaphy. *Br J Anaesth* 1999; **82**: 280–2

14 Benhamou D, Hamza J, Eledjam JJ, Dailland P, Palot M, Seebacher J, Milon D, Heeroma K. Continuous extradural infusion of ropivacaine 2 mg ml^{-1} for pain relief during labour. *Br J Anaesth* 1997; **78**: 748–50

15 Bertini L, Tagariello V, Mancini S, Ciaschi A, Posteraro CM, Di Benedetto P, Martini O. 0.75% and 0.5% ropivacaine for axillary brachial plexus block: A clinical comparison with 0.5% bupivacaine. *Reg Anesth Pain Med* 1999; **24**: 514–8

16 Boogaerts JG, Lafont ND, Declercq AG, Luo HC, Gravet ET, Bianchi JA, Legros FJ. Epidural administration of liposome-associated bupivacaine for the management of postsurgical pain: a first study. *J Clin Anesth* 1994; **6**: 315–20

17 Brinklov M. Clinical effects of carticaine, a new local anaesthetic. *Acta Anaesthesiol Scand* 1977; **21**: 5–16

18 Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *Br J Anaesth* 1991; **66**: 31–7

19 Brown DL, Carpenter RL, Thomson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; **72**: 633–6

20 Buchi J, Perlia X. Structure-activity relations and physiochemical properties of local anesthetics. In: *International Encyclopaedia of Pharmacology and Therapeutics, Section 8, Vol. 1, Local Anesthetics.* Oxford: Pergamon Press, 1971; 39–130

21 Burke D, Joypaul V, Thomson MF. Circumcision supplemented by dorsal penile nerve block with 0.75% ropivacaine: a complication. *Reg Anesth Pain Med* 2000; **25**: 424–7

22 Burke D, MacKenzie M, Newton D, Khan F, McLeod GA, Belch J, Bannister J. A comparison of the vasoactivity between levobupivacaine and bupivacaine (abstract). *Br J Anaesth* 1998; **81**: 631–2P

23 Burke D, Kennedy S, Bannister J. Spinal anaesthesia with 0.5% S(–)-bupivacaine for elective lower limb surgery. *Reg Anesth Pain Med* 1999; **24**: 519–23

24 Burke D, Henderson DJ, Simpson AM, Faccenda KA, Morrison LMM, McGrady EM, McLeod GA, Bannister J. Comparison of 0.25% S(–)-bupivacaine with 0.25% RS-bupivacaine for epidural analgesia in labour. *Br J Anaesth* 1999; **83**: 750–5

25 Cahn RS, Ingold CK, Pelog V. The specification of asymmetric configuration in organic chemistry. *Experentia* 1956; **12**: 81–124

26 Campbell DC, Zwack RM, Crone LA, Yip RW. Ambulatory labor epidural analgesia: bupivacaine versus bupivacaine. *Anesth Analg* 2000; **90**: 1384–9

27 Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**: 371–3

28 Cederholm I, Åckerman B, Evers H. Local analgesic and vascular effects of intradermal ropivacaine and bupivacaine in various concentrations with and without adrenaline in man. *Acta Anaesthesiol Scand* 1994; **38**: 322–7

29 Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiovascular conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology* 1985; **62**: 396–405

30 Columb MO, Lyons G. Determination of the minimum local analgesic concentration of epidural bupivacaine and lidocaine in labor. *Anesth Analg* 1995; **81**: 833–7

31 Concepcion M, Arthur GR, Steele SM, Bader AM, Covino BG. A new local anesthetic, ropivacaine. Its epidural effects in humans. *Anesth Analg* 1990; **70**: 80–5

32 Convery PN, Milligan KR, Weir P. Comparison of 0.125% levobupivacaine and 0.125% bupivacaine epidural infusions for labour analgesia (abstract). *Br J Anaesth* 1999; **82**(suppl. 1): 163

33 Covino BG, Wildsmith JAW. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain.* Philadelphia: Lippincott-Raven, 1998; 97–128

34 Cox CR, Checketts MR, MacKenzie N, Scott NB, Bannister J. Comparison of S(–)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. *Br J Anaesth* 1998; **80**: 594–8

35 Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LMM. Extradural S(–) bupivacaine: comparison with racemic RS-bupivacaine. *Br J Anaesth* 1998; **80**: 289–93

36 Dahl JB, Simonsen L, Mogensen T, Henriksen JH, Kehlet H. The effect of 0.5% ropivacaine on epidural blood flow. *Acta Anaesthesiol Scand* 1990; **34**: 308–10

37 D'Angelo R, James RL. Is ropivacaine less potent than bupivacaine ? *Anesthesiology* 2000; **92**: 283–4

38 Djordjevich L, Ivankovich AD, Chiguupati R, Woronowicz A, McCarthy R. Efficacy of liposome encapsulated bupivacaine. *Anesthesiology* 1986; **65**: A185

39 Duncan LA, Wildsmith JAW. Liposomal local anaesthetics [editorial]. *Br J Anaesth* 1995; **75**: 260–1

40 Eddleston JM, Holland JJ, Griffin RP, Corbett A, Horsman EL, Reynolds F. A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour. *Br J Anaesth* 1996; **76**: 66–71

41 Erichsen CJ, Vibits H, Dahl JB, Kehlet H. Wound infiltration with ropivacaine and bupivacaine for pain after inguinal herniotomy. *Acta Anaesthesiol Scand* 1995; **39**: 67–70

42 Ericsson AC, Avesson M. Effects of ropivacaine, bupivacaine and S(–) bupivacaine on the ECG after rapid IV injections to conscious rats. *Int Monitor Reg Anaesth* 1996; **8**: 51

43 Fanelli G, Casati A, Beccaria P, *et al.* A double-blind comparison of ropivacaine, bupivacaine, and mepivacaine during sciatic and femoral nerve blockade. *Anesth Analg* 1998; **87**: 597–600

44 Federsel H, Jaksch P, Sanberg R. An efficient synthesis of a new, chiral 2′,6′-pipecoloxylidide local anaesthetic agent. *Acta Chemica Scandanavica* 1987; **B41**: 757–61

45 Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. *Anesth Analg* 1991; **73**: 373–84

46 Feldman HS, Covino B. Comparative motor blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. *Anesth Analg* 1988; **67**: 1047–52

47 Finucane BT. Ropivacaine: epidural anesthesia for surgery. *Am J Anesthesiol* 1997; **24**: 22–5

48 Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as alocal anaesthetic. *Drugs* 2000; **59**: 551–79

49 Friedman GA, Rowlingson JC, DiFazio CA, Donegan MF. Evaluation of the analgesic effect and urinary excretion of sytemic bupivacaine in man. *Anesth Analg* 1982; **61**: 23–7

50 Gatt S, Crooke S, Lockley S, Anderson A, Armstrong P, Alley L. A double-blind, randomized parallel investigation into the neurobehavioural status and outcome of infants born to mothers receiving epidural ropivacaine 0.25% and bupivacaine 0.25% for analgesia in labour. *Anaesth Intensive Care* 1996; **24**: 108–9

51 Gautier PE, De Kock M, Van Steenberge A, *et al.* Intrathecal ropivacaine for ambulatory surgery: A comparison between intrathecal bupivacaine and ropivacaine for knee surgery. *Anesthesiology* 1999; **91**: 1239–45

52 Gautier P, De Kock M, van Steerbridge A, Miclot D, Fanard L, Hody JL. A double-blind comparison of 0.125% ropivacaine with sufentanil and 0.125% bupivacaine with sufentanil for epidural labor analgesia. *Anesthesiology* 1999; **90**: 772–8

53 Grant GJ, Vermuelen K, Langerman L, Zakowski M, Turndorf H. Prolonged analgesia with liposomal bupivacaine in a mouse model. *Reg Anesth Pain Med* 1994; **19**: 264–9

54 Griffin RP, Reynolds F. Extradural anaesthesia for caesarian section: a double-blind comparison of 0.5% ropivacaine and 0.5% bupivacaine. *Br J Anaesth* 1995; **74**: 512–6

55 Haas D, Harper D, Saso M, Young E. Comparison of articaine and prilocaine anesthesia in maxillary and mandibular arches. *Anesth Prog* 1990; **37**: 230–3

56 Hickey R, Blanchard J, Hoffman J, Sjövall J, Ramamurthy S. Plasma concentrations of ropivacaine given with or without epinephrine for brachial plexus block. *Can J Anaesth* 1990; **37**: 878–82

57 Hickey R, Candido KD, Ramamurthy S, *et al.* Brachial plexus block with a new local anaesthetic: 0.5% ropivacaine. *Can J Anaesth* 1990; **37**: 732–8

58 Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. *Anesthesiology* 1991; **74**: 639–642

59 Hickey R, Rowley CL, Candido KD, Hoffman J, Ramamurthy S, Winnie AP. A comparative study of 0.25% ropivacaine and 0.25% bupivacaine for brachial plexus block. *Anesth Analg* 1992; **75**: 602–6

60 Huang YF, Pryor ME, Veering BT, Mather LE. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *Anesth Analg* 1998; **86**: 797–804

61 Johansson B, Glise H, Hallerback B, Dalman P, Kristofferson A. Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. *Anesth Analg* 1994; **78**: 210–4

62 Katz JA, Knarr D, Bridenbaugh PO. A double-blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. *Reg Anesth Pain Med* 1990; **15**: 250–2

63 Kerkkamp HEM, Gielen MJM, Edström HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anaesthesia. *Reg Anesth Pain Med* 1990; **15**: 204–7

64 Kingsnorth A, Bennet D, Cummings C. A randomised, double blind study to compare the efficacy of 0.25% levobupivacaine with 0.25% bupivacaine (racemic) infiltration anaesthesia in elective inguinal hernia repair. *Reg Anesth Pain Med* 1998; **23**(suppl.): 106

65 Knudsen K, Beckman-Suurkula M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14

66 Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989; **71**: 69–74

67 Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesth Analg* 2000; **90**: 642–8

68 Korsten HH, Ackerman EW, Grouls RJ, *et al.* Long-lasting sensory blockade by n-butyl-p-aminobenzoate in the terminally ill intractable cancer pain patient. *Anesthesiology* 1991; **75**: 950–60

69 Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. *Arch Int Pharmacodyn* 1972; **200**: 359–69

70 Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; **81**: 899–901

71 Mashimo T, Uchida I, Pak M, *et al.* Prolongation of canine epidural anesthesia by liposome encapsulation of lidocaine. *Anesth Analg* 1992; **74**: 827–34

72 Mazoit JX, Boico O, Samii K. Myocardial uptake of bupivacaine: pharmacodynamics of bupivacaine enantiomers in the isolated perfused rabbit heart. *Anesth Analg* 1993; **77**: 477–82

73 McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76**: 300–7

74 McClure JH. The obstetric challenge. *Am J Anesthesiol* 1997; **24** (5; Suppl): 18–21

75 McCrae AF, Jozwiak H, McClure JH. Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour. *Br J Anaesth* 1995; **74**: 261–5

76 McCrae AF, Westerling P, McClure JH. Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour. *Br J Anaesth* 1997; **79**: 558–62

77 McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine: A comparison to bupivacaine in volunteers. *Anesthesiology* 1999; **90**: 971–77

78 Moller R, Covino BG. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with thosw of ropivacaine, a new amide local anaesthetic. *Anesthesiology* 1990; **72**: 322–9

79 Morrisson LMM, Emanuelsson BM, McClure JH, *et al.* Efficacy and kinetics of extradural ropivacaine: Comparison with bupivacaine. *Br J Anaesth* 1994; **72**: 269–73

80 Mulroy MF, Burgess FW, Emanuelson BM. Ropivacaine 0.25% and 0.5%, but not 0.125% provide effective wound infiltration analgesia after outpatient hernia repair, but sustained plasma drug levels. *Reg Anesth* 1999; **23**: 136–41

81 Nolte H, Fruhstorfer H, Edström HH. Local anaesthetic efficacy of ropivacaine (LEA 103) in ulnar nerve block. *Reg Anesth Pain Med* 1990; **15**: 118–24

82 Owen MD, D'Angelo R, Gerancher JC, Thompson JM, Foss ML, Babb JD, Eisenach JC. 0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion. *Anesth Analg* 1998; **86**: 527–31

83 Pitkanen M, Covino BG, Feldman HS, Arthur GR. Chronotropic and inotropic effects of ropivacaine, bupivacaine and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. *Reg Anesth* 1992; **17**: 183–92

84 Polley LS, Columb MO, Naughton NN, Wagner DS, Cosmas JM. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labour. *Anesthesiology* 1999; **90** 944–50

85 Reiz S, Haggmark S, Johansson G, Nath S. Cardiotoxicity of ropivacaine – a new amide local anaesthetic agent. *Acta Anaesthesiol Scand* 1989; **33**: 93–8

86 Rosenberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics. *Br J Anaesth* 1983; **55**: 163–7

87 Santos AC, Karpel B, Noble G. The placental transfer and fetal effects of levobupivacaine, racemic bupivacaine and ropivacaine. *Anesthesiology* 1999; **90**: 1698–703

88 Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

89 Scrutton MJ, Srikantharajah L, Williams H, Porter J, O'Sullivan G. Comparison of ropivacaine with bupivacaine for epidural analgesia in labour. *Anesthesiology* 1994; **90** (suppl.): A34

90 Simon MA, Vree TB, Gielen MJ, Booij LH. Comparison of the effects and disposition kinetics of articaine and lidocaine in 20 patients undergoing intravenous regional anaesthesia during day case surgery. *Pharm World Sci* 1998; **20**: 88–92

91 Shulman M. Treatment of cancer pain with epidural Butyl-Amino-Benzoate suspension. *Reg Anesth Pain Med* 1987; **12**: 1–4

92 Shulman M, Lubenow TR, Nath HA, Blazek W, McCarthy RJ, Ivankovich AD. Nerve blocks with 5% butamben suspension for the treatment of chronic pain syndromes. *Reg Anesth Pain Med* 1998; **23**: 395–401

93 Stienstra R. A closer look at the new local anesthetics. *Acta Anaesth Belg* 1999; **50**: 211–6

94 Tetzlaff JE. Ropivacaine. In: Tetzlaff JE, ed. *Clinical Pharmacology of Local Anesthetics*. Boston: Butterworth Heinemann, 2000; 125–31

95 Tucker GT. Ropivacaine: human pharmacokinetics *Am J Anesthesiol* 1997; **24** (5; Suppl): 8–13

96 Vainionpää VA, Haavisto ET, Huha TM, Korpi KJ, Nuutinen LS, Hollmén AI, Jozwiak HM, Magnusson M. A clinical and pharmacokinetic comparison of ropivacaine and bupivacaine in axillary plexus block. *Anesth Analg* 1995; **81**: 534–8

97 Valenzuela C, Delpon E, Perez O, Tamkun MM, Tamargo J, Snyders DJ. Stereoselective bupivacaine block of human cardiac delayed rectifier hKv1.5 channel. *Biophys J* 1994; **66**: A205

98 van Kleef JW, Veering BT, Burm AGL. Spinal anaesthesia with ropivacaine: a double-blind study on the efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. *Anesth Analg* 1994; **78**: 1125–30

99 Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E. Stereoselective effects of the enantiomers of bupivacaine on electrophysiological properties of the guinea-pig papillary muscle. *Br J Pharmacolol* 1991; **103**: 1275–81

100 Wahedi W, Nolte H, Klein P. Ropivacaine in spinal anaesthesia. *Anaesthesist* 1996; **45**: 737–44

101 Whitehead E, Arrigoni B, Bannister J. An open study of ropivacaine in extradural anaesthesia. *Br J Anaesth* 1990; **64**: 67–71

102 Whiteside JB, Burke D, Wildsmith JAW. Spinal anaesthesia with ropivacaine 5 mg ml^{-1} in glucose 10 mg ml^{-1} or 50 mg ml^{-1}. *Br J Anaesth* 2001; **86**: 241–4

103 Wildsmith JAW, Brown DT, Paul D, Johnson S. Structure-activity relationships in differential nerve block at high and low frequency stimulation. *Br J Anaesth* 1989; **63**: 444–52

104 Wildsmith JAW. Peripheral nerve block and ropivacaine. *Am J Anesthesiol* 1997; **24** (5; Suppl): 14–17

105 Wildsmith JAW. Relative potencies of ropivacaine and bupivacaine. *Anesthesiology* 2000; **92**: 283

106 Winther JE, Patirupanusara B. Evaluation of carticaine – a new local analgesic. *Int J Oral Surg* 1974; **3**: 422–7

107 Wolff AP, Hasselstrom L, Kerkkamp HE, Gielen MJ. Extradural ropivacaine and bupivacaine in hip surgery. *Br J Anaesth* 1995; **74**: 458–60

108 Wood MB, Rubin AP. A comparison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynaecological surgery. *Anesth Analg* 1993; **76**: 1274–8

109 Writer WDR, Stienstra R, Eddleston JM, *et al.* Neonatal outcome and mode of delivery after epidural analgesia for labour with ropivacaine and bupivacaine: a prospective meta-analysis. *Br J Anaesth* 1998; **81**: 713–7

110 Yamashiro H. Bupivacaine-induced seizure after accidental intravenous injection, a complication of epidural anesthesia. *Anesthesiology* 1977; **47**: 472–3

111 Zaric D, Axelsson K, Nydahl PA, Philipsson L, Larsson P, Jansson JR. Sensory and motor blockade during epidural analgesia with 1.0%, 0.75% and 0.5% ropivacaine – a double-blind study. *Anesth Analg* 1991; **72**: 509–15

112 Zaric D, Axelsson K, Nydahl PA, Philipsson L, Samuelsson L. Sensory and motor blockade during continuous epidural infusion of ropivacaine 0.1%, 0.2% and 0.3% in volunteers – a double-blind study. *Reg Anesth Pain Med* 1994; **19**(Suppl 2S): 60

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Safety and efficacy of patient-controlled analgesia

P. E. Macintyre

Acute Pain Service, Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital and University of Adelaide, North Terrace, Adelaide, SA 5000, Australia

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In a general sense, patient-controlled analgesia (PCA) refers to a process where patients can determine when and how much medication they receive, regardless of analgesic technique. However, the term is more commonly used to describe a method of pain relief which uses disposable or electronic infusion devices and allows patients to self-administer analgesic drugs, usually intravenous (i.v.) opioids, as required. The main focus of this review will be i.v. PCA.

The overall effectiveness of any analgesic technique depends on both the degree of pain relief that can be achieved and the incidence of side effects or complications. Therefore, factors affecting efficacy and safety of PCA are often inextricably linked. This review will consider:

- analgesic efficacy—compared with conventional methods of pain relief in post-operative patients (including pain relief, analgesic use and cost comparisons), when used in non-surgical patients, and with opioid administration by other than the i.v. route;
- patient outcomes—patient satisfaction and post-operative morbidity;
- patient factors that may affect safety and efficacy—including patient age, psychological characteristics, concurrent disorders, opioid tolerance, and inappropriate use of PCA;
- equipment factors that may affect safety and efficacy—including equipment design and malfunction;
- medical and nursing staff factors;
- the PCA 'prescription'—including programmable variables and drugs used.

Analgesic efficacy

In 1993, a paper by Ballantyne and colleagues[3] reported on the results of a meta-analysis, which was designed to examine the evidence in published randomized controlled trials comparing clinical outcomes of PCA and conventional intramuscular (i.m.) analgesia. They included studies comparing i.v. PCA (without a concurrent continuous infusion) with i.m. opioid analgesia ordered 3–4 hourly PRN. Exclusion criteria included studies in special patient populations (e.g. children and elderly patients) and patients who routinely received intensive care post-operatively (e.g. after cardiac surgery). Significantly greater analgesic efficacy was seen with PCA, although the magnitude of the difference was small (just 5.6 on a pain scale of 0–100).

Some of the more recent studies comparing PCA with conventional methods of opioid analgesia, administered as intermittent i.m.,[8 12 16 90] subcutaneous (s.c.)[60] and i.v. injections,[6 93] or by continuous infusion,[34 61] have produced contradictory results. Some show significantly better analgesia with PCA[6 34 90] and others report no difference.[8 12 60 61 93]. Colwell and Morris[16] noted better analgesia after i.m. morphine. However, PCA bolus doses used in their study were small, 0.25 or 0.5 mg morphine, while patients in the i.m. group could receive up to 15 mg morphine every 3 h if required. Sample sizes in many of these studies are small and difference, or lack of difference, could be difficult to detect.

Given the continuing popularity of PCA, these results could be seen as surprising. However, it is possible, if analgesia can truly be given 'on demand', with doses and appropriate dose intervals tailored to the individual patient, that good results can be obtained regardless of analgesic technique.

Of the studies listed above, in which no difference was found in analgesic efficacy, three[60 61 93] examined pain relief in patients after cardiac surgery. These patients were nursed in intensive care settings where there are usually higher nurse:patient ratios than in general hospital wards. In such settings, it may be easier to provide closer nursing supervision and analgesia when required and with minimal delay. Pettersson and colleagues[71] also compared analgesic efficacies of PCA and nurse-managed i.v. opioids in patients

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after cardiac surgery. They found that pain relief using PCA was comparable with that obtained from an infusion while patients were in intensive care (1:1 nurse:patient ratio). However, when the patients were transferred to a general ward, significantly better analgesia was obtained with PCA than with intermittent i.v. bolus doses of opioid.

Whether a study is performed in an intensive care or general ward setting, it is also possible that efficacy may improve because of the study environment. The close interest shown by investigators could lead to greater nursing attention paid to conventional methods of pain relief—the 'Hawthorn' effect.[100] In a busy ward setting, the use of an electronically-controlled device may merely facilitate more immediate drug delivery.

In most studies, pain scores are carried out intermittently, often on a 2 or 4 hourly basis and sometimes only once or twice a day, and unrelated to the timing of drug administration. It has been suggested that this could 'understate the benefit of PCA'[3] as PCA allows a more flexible matching of analgesic delivered and patient need.

Analgesic use

In their meta-analysis, Ballantyne and colleagues[3] reported a non-significant trend towards lower opioid use in PCA patients. In 10 studies looking at differences in use, PCA opioid requirements were significantly higher in one; i.m. requirements were significantly higher in four.

Studies since then have continued to produce conflicting results, with some authors reporting significantly higher opioid use with PCA,[6 34 71] significantly higher use with conventional methods of opioid analgesia,[12 16 90] or no difference.[8 61]

Whether or not there are differences in opioid use, most studies report similar incidences of nausea and vomiting,[3 6 12 16 34 60 61 71] sedation,[3 6 16 34 71] pruritus,[12 60] and bowel function.[6 8 12 16] In view of these findings, total opioid dose may be relatively unimportant.

It is harder to compare the incidence of respiratory depression between PCA and conventional methods of opioid analgesia. This is partly because the risk is small and, therefore, most, if not all, studies would have inadequate numbers of patients in each group to be able to show a significant difference. In addition, the definitions of respiratory depression vary widely. Many authors choose to define respiratory depression as a respiratory rate of less than 8 or 10 breaths min^{-1}, even though a decrease in respiratory rate is known to be an unreliable indicator of the presence or absence of respiratory depression.[26 62 101] A better clinical indicator of early respiratory depression is sedation, and many centres routinely monitor patient sedation using sedation scores.[62] Better estimates of the risk of respiratory depression with PCA are obtained from results of larger audits (see later).

Cost comparisons

Costs involved in the provision of analgesia, including the direct costs of drugs, consumables, equipment, and labour, are important when considering whether or not to use a particular method of pain relief, even if it is more effective. Jacox and colleagues[42] reviewed seven studies published from 1984 to 1995 which compared costs related to PCA and i.m. opioid analgesia. They concluded that while PCA may provide superior analgesia and patient satisfaction, it does so at a higher cost. Similar results have been reported by other authors.[12 19] A comparison of the differences in cost across the studies is difficult as they vary with respect to patient population, organization of PCA management, PCA device involved, drugs administered, and methods used to determine expenses.

A significant part of the cost of PCA is the cost of equipment, drugs, and consumables. Nursing time (time involved in the provision of analgesia) is usually much less compared with conventional forms of pain relief.[12 16 19] Therefore, in a busy general hospital ward where the number of appropriately qualified nurses may be limited, it is possible that the use of PCA in some patients may allow more time to attend to other duties, including the more effective provision of other forms of analgesia to patients without PCA.

In view of the current need in most countries to control health care costs, a decrease in average length of stay (ALOS) in hospital also has important implications. However, no difference between PCA and i.m. opioid analgesia was found by Ballantyne and colleagues[3] (although two studies included in this meta-analysis found that PCA was associated with a lower ALOS). Later studies have confirmed this lack of difference.[12 16]

Efficacy in non-surgical patients

PCA is most commonly used in the management of post-operative and post-injury pain. However, it has been shown to be effective in the management of pain from other causes such as sickle cell crises,[98] burns injury,[11] oral mucositis after bone marrow transplantation,[21] cancer pain,[97] extra-corporeal shock wave lithotripsy[79] and angina,[59] and as an investigative tool, often used to compare drugs and techniques.

Efficacy via non-i.v. routes

Opioid self-administration has also been shown to be effective using other routes including s.c.[18 95 104], oral,[87] and intranasal routes[91]. Epidural PCA is discussed by Wheatley and colleagues in their article in this issue of the journal.[102]

Dawson and colleagues[18] compared s.c. and i.v. PCA diamorphine and reported that patients using s.c. PCA experienced significantly less pain and less sleep disturbance. Urquhart and others[95] and White[104] recorded no significant difference in pain scores using hydromorphone,[95] morphine,[104] or oxymorphone.[104] Interestingly, all three studies reported significantly higher opioid requirements with the use of s.c. PCA compared with i.v. PCA. No difference in nausea and vomiting was found in two of the studies[18 95] while an increased incidence was noted in the other study[103] in association with s.c. PCA.

Oral (using an adapted disposable PCA device)[87] or intranasal[91] PCA appears to be as effective as i.v. PCA.

Potential to mask post-operative complications

Concerns have been expressed by some that PCA may be 'too efficacious' as the patient can self-administer opioid to treat any pain they are experiencing. For example, there have been reports of PCA 'masking' signs of urinary retention,[39] compartment syndrome,[37] pulmonary embolism,[58] and myocardial infarction.[28]

In the case described by Harrington and colleagues,[37] compartment syndrome was not detected until the patient returned for a second operation, 36 h after initial surgery for lower limb trauma. PCA was commenced after the first operation. However, it would appear that the patient was monitored (hourly pain and sedation scores) for the first 6 h only and that these observations were not repeated regularly during the last 30 h of PCA therapy. Despite their concerns about PCA, the authors concluded that this technique might be a 'perfectly acceptable means' of providing post-operative analgesia in patients with lower limb trauma if hourly patient monitoring is continued throughout the duration of therapy.

The concern expressed in these case reports is that PCA allows the patient to increase opioid use to cover any 'new' pain without informing nursing or medical staff. However, in post-operative patients, assessment of pain and opioid use should be regular and frequent. As most PCA treatment regimens incorporate such assessments, often on a 1- or 2-hourly basis, it could be argued that PCA might allow a more accurate measure of pain and increases in opioid dose. Any unexpected change in analgesic use, or the site, severity or character of the pain being treated, warrants careful investigation, as it may signal the development of a new surgical or medical diagnosis.[62]

Patient outcomes

Patient satisfaction

In their meta-analysis, Ballantyne and colleagues[3] concluded that there was 'considerable evidence' of higher patient satisfaction with PCA compared with i.m. opioids. Once again, there have been conflicting results in some of the studies performed since. Both better patient satisfaction with PCA[6] and no difference compared with conventional methods of opioid administration[8 12] have been reported.

Satisfaction ratings are often considered to be an important outcome in health care and an indication of the patients' view of efficacy. However, evaluation of satisfaction is complex and it is known that patient satisfaction surveys tend to produce positive results because patients are reluctant to criticize their treatment.[14]

Although there appears to be a correlation between satisfaction and lower pain intensity,[43 69] many patients who experience quite high levels of pain will also report satisfaction with pain management.[14 15 70] Many patients still expect severe pain after surgery and may be quite pleased to find that it is not as bad as expected.[27]

Other factors that have been shown to have a significant association with higher satisfaction ratings include perceived control,[69] and lower pre-operative anxiety and post-operative depression.[43] A correlation between perceived control and good pain relief has also been reported.[14 69]

As the inverse association between patient satisfaction and pain intensity is small, there must be other additional reasons why satisfaction with PCA is high compared with conventional methods of opioid analgesia. A number of positive aspects about the PCA experience have been identified, in addition to control over pain relief.[14 45] These include not having to wait for pain relief,[14 45 88] not having injections,[14 45] and not having to bother nurses.[14 45 88]

Negative aspects about PCA have also been identified, some of which might constrain the use of PCA and, hence, it's effectiveness. Most often the negative remarks relate to inadequate analgesia and/or the presence of side effects,[14 88] but some patients also report not trusting the PCA machine,[14 45] or fearing overdose,[14 45 88] or addiction.[14 45 88] Chumbley and colleagues[14] reported that 22% of patients feared addiction and 30% feared overdose, much higher than the 4 and 11%, respectively, reported by Kluger and Owen.[45] However, 43% of patients in the former study did not receive pre-operative education about PCA (and 24% received no instruction at all at any time during PCA therapy), whereas all patients in the latter study received education about pain management and PCA prior to surgery. Chumbley and colleagues[14] noted that lack of education was associated with higher pain ratings.

Effect on post-operative morbidity

In general, the analgesic technique associated with the greatest improvements in post-operative morbidity, particularly with respect to pulmonary complications,[4] is epidural analgesia, which is discussed in the article by Wheatley in this issue of the journal.[102]

The meta-analysis by Ballantyne and colleagues[3] included three studies that looked at bowel function (time to first flatus or stool) and three that looked at pulmonary function. No differences were found between PCA and i.m. analgesia. Later studies have shown that PCA use, in comparison with conventional methods of opioid administration, may be associated with a lower incidence of atelectasis,[34] higher VC and FEV_1[6] or no difference in FEV_1,[93] thus, the evidence is still unconvincing.

Post-operative morbidity related to the side effects of the drugs prescribed is discussed briefly later.

Patient factors

Patient-related factors, including age, psychological characteristics, concurrent disorders, opioid dependency, and inappropriateness of PCA use, may have a significant influence on the safety and efficacy of PCA.

Patient age

Although very young and very old patients may be less likely to manage PCA successfully, PCA should not be withheld simply on the basis of age.[27 54] Children as young as 4 yr old[21] to patients in their late 90s[54] have been reported to use PCA effectively.

Egbert and co-workers[25] compared PCA with i.m. morphine analgesia in elderly men. PCA resulted in better pain relief, less confusion and fewer severe pulmonary complications. The incidence of 'significant' confusion was only 2.3% in patients receiving PCA compared with 18% in those given i.m. analgesia. They noted that 17.5% of PCA patients had problems initiating bolus doses on first day because of mild confusion. However, 28% of i.m. patients failed to request injections appropriately for the same reason and, therefore, all elderly patients should be followed closely to ensure that they are getting adequate pain relief.

The successful use of PCA requires reasonably normal cognitive function and patients who have pre-operative evidence of dementia or become confused post-operatively (more likely in the elderly patient[48]) are not suitable candidates for PCA.[25 48]

Post-operative PCA opioid requirements in adults are known to decrease as patient age increases,[53] and it has, therefore, been suggested that a lower PCA bolus dose is prescribed for elderly patients.[27 48 53] Concurrent use of a background infusion is contraindicated in these patients, if they are opioid-naive. [27 48]

Psychological characteristics

The subjective experience of pain is dependent on a number of factors, including patients' psychological characteristics. These include state anxiety (a transitory state which varies in intensity and over time, and is associated with specific situations involving threat), trait anxiety (a personality disposition which is relatively stable over time), neuroticism, and coping style.[90] These characteristics may affect how well patients make use of PCA and, therefore, its effectiveness, and should be taken into account when patients are considered for this form of pain relief.

Anxiety seems to be the most important psychological measure affecting PCA use[32] and high levels of anxiety are significantly related to higher pain scores in patients using PCA,[32 70 90] although it appears that state rather than trait anxiety may be the better predictor of pain in this circumstance.[70 90] High levels of anxiety may also be associated with more frequent unsuccessful PCA demands, that is, demands during the 'lockout' period, which do not result in increased opioid use.[32 43]

Concurrent disorders

A number of concurrent patient diseases or conditions may need to be taken into account when PCA is prescribed. For example, renal impairment may affect excretion of the metabolites of morphine, leading to respiratory depression,[74] and pethidine, leading to norpethidine toxicity.[31] Hypovolaemia may also increase the risk of respiratory depression.[26]

Concerns have also been raised about the use of PCA in patients who are morbidly obese or who have obstructive sleep apnoea (OSA).[26 81 96] A near-fatal case of respiratory depression was reported by VanDercar and colleagues[96] associated with PCA use in a patient with OSA. However, the PCA machine was set to deliver a background infusion as well as patient demand doses.

PCA, without a background infusion, has been used safely and effectively for pain relief after abdominal surgery in morbidly obese patients,[10 47 50] up to 40% of whom may have OSA[47]. If patients are known to have OSA, more intensive monitoring and judicious use of PCA (e.g. use of a smaller initial bolus dose) have been suggested.[27 50]

Opioid-tolerant patients

Patients with a history of opioid consumption (whether legally prescribed or illegally obtained) before admission to hospital may be dependent on these drugs (that is they will exhibit signs of withdrawal if the drug is suddenly stopped or antagonized) and may show signs of tolerance to both their analgesic effects and side effects.[54 62]

Rapp and colleagues[73] compared PCA use after surgery in opioid-tolerant patients (patients with cancer pain, chronic non-cancer pain, and those with an opioid addiction) and in opioid-naive control patients. They concluded that patients with previous exposure to opioids were likely to have higher opioid requirements (total doses averaged three times those of opioid-naive patients), higher pain scores, and fewer emetic and pruritic symptoms. Surprisingly, sedation scores were higher in the opioid-tolerant patients. Although patients in this group were much more likely to be given concurrent anxiolytics, the authors state that this did not correlate with increased sedation. This suggests that if opioid doses can be rapidly increased to levels significantly in excess of pre-admission basal doses, oversedation (a better clinical indicator of early respiratory depression than a decrease in respiratory rate—see above[62]) may occur in patients who are considered to be tolerant to effects of the drugs.

Significant deviation from 'standard' PCA prescriptions may be needed in opioid-tolerant patients if effective analgesia is to be obtained. Background infusions can be used to deliver the equivalent of the patient's basal opioid dose, if the patient is unable to take their usual opioid.[27 54] The size of the bolus dose will often need to be increased; a dose based on calculated hourly background dose has been suggested.[27 54]

Addiction to opioids was initially thought to be a contraindication to the use of PCA, but it is now recognized to be a useful method of providing pain relief.[62] This may be partly because these patients may have high and unpredictable opioid requirements, and partly because it helps to avoid staff/patient confrontations about dose and dose interval. As these patients are more likely to report high pain scores, a functional assessment of pain relief (e.g. ability to cough, ambulation) may be required in addition to patient self-reports when determining efficacy of analgesia.[73]

Inappropriate use of PCA

The safety of PCA depends on an adequate understanding of the technique by the patient and the fact that unauthorized persons do not press the demand button.

Oversedation with PCA has followed repeated use at the end of every lockout period (patient misunderstanding of pre-operative explanation),[83] mistaking the PCA handset for the nurse-call button,[94] and family,[2 29 81 80] visitor,[9] or unauthorized nurse-activated demands.[29 101]

Equipment factors

Electronic and disposable infusion devices are both used in the provision of PCA. Each type has two components—a reservoir and a patient-control module. Although equipment-related PCA complications are less common than operator-related or drug-related problems, device design and malfunction may affect analgesic efficacy and patient safety. Problems may also arise with PCA-related consumables.

Disposable PCA devices

Disposable PCA devices typically deliver 0.5 ml with each patient demand, take about 6 min for the patient-control module to refill from a reservoir, and deliver no more than 0.5 ml every 6 min, should the demand button be depressed continuously.[75 76] Efficacy and side effects may be comparable with the electronic devices.[75] However, as the device delivers a fixed volume with each demand, the amount of drug delivered in each bolus can only be altered by changing the concentration of drug in the reservoir. In addition, the opioid in the reservoir is much more easily accessible than that in locked electronic infusion devices.

Few significant problems as a result of malfunction have been identified. One of the more potentially serious episodes is that reported by Costigan,[17] where the absence of an 'O' ring allowed unrestricted flow of opioid from the reservoir. Fortunately, this was noticed before the device was attached to the patient.

Electronic PCA devices

Electronic PCA devices allow more flexibility in the timing and amount of dose delivered. They can also be programmed to deliver a constant background infusion. They are designed to be 'tamper proof', so that access to the drug without using the key is impossible, at least unless the pump is damaged in the attempt. However, successful access has been achieved without machine breakage (unpublished observations). Reports of problems related to the use of electronic PCA devices seem to be more common, although that may reflect usage patterns.

These devices should 'fail safe' if any corruption to the program occurs. Reports in the literature describe 'fail safe' electrical corruption of the pump program as a result of disconnection from, or reconnection to, mains power.[41 64] In some instances, however, the machines did not 'fail safe'. This led to spontaneously triggered bolus doses[64] or uncontrolled delivery of the entire syringe contents.[63] Modifications to both hardware and software appear to have overcome these problems in later machines,[41] although a report of repeated spontaneous triggering was published recently.[13]

Problems that allowed uncontrolled syphoning of syringe contents have also been reported, including failure of a damaged drive mechanism to retain the syringe plunger,[46] cracked glass PCA syringes,[23 89] and improperly secured PCA cassettes.[22] In all these instances, the PCA machine was elevated above the patient. Although placing the machine at or below patient heart level may minimize the risk of syphoning occurring,[89] the use of antisyphon valves, as well as antireflux valves, has been suggested.[23 36] The routine use of antireflux valves has been recommended for many years[44] but a respiratory arrest has resulted from a recent failure to use such a valve.[68] Faulty antireflux valves have also been reported.[64 103]

Other causes of equipment-related problems include patient tampering,[2] an excessive dose of opioid being delivered accidentally when tubing from the PCA syringe was not clamped while a new syringe was loaded[103] and the use of pumps close to an MRI machine[49] or in a hyperbaric chamber.[78]

Medical and nursing staff factors

Operator errors have led to oversedation resulting from the programming of incorrect bolus dose size,[103] incorrect drug concentrations (with fatal results),[24] incorrect background infusions[38] and background infusions when none were ordered.[2] It has been suggested that drug concentrations should be standardized within institutions to reduce the chance of program errors.[42 80]

Operator error is a reasonably common type of safety problem related to PCA use. Lin and colleagues,[51] believing that poorly designed interfaces promote human errors, used a human factors approach (which takes into account human capabilities and limitations) to redesign the user interface of a PCA machine. This resulted in significantly faster programming times and significantly fewer programming errors. They recommended that the task of interfacing with the machine should be made as transparent as possible and that human factors principles should be taken into account in the design and evaluation of medical equipment, as ease of use is just as important as reliability of delivery.

Incorrect checking procedures may lead to the 'wrong' syringe being placed in a PCA pump—for example, a syringe of bupivacaine and fentanyl intended for epidural use, and one of plain fentanyl intended for PCA, have been used for i.v. PCA, when morphine was ordered in both cases (unpublished observations).

The level of knowledge that nursing and medical staff have about PCA may also play a role in its safety and efficacy. The study by Coleman and Booker-Milburn[15] showed that the introduction of an acute pain service (APS) nurse, whose role included staff and patient education, led to improvements in analgesia and patient satisfaction with PCA and an increased use of oral analgesia after PCA therapy was stopped.

A study comparing PCA managed by an APS compared with surgeons in the same hospital but 1 yr later, revealed that patients whose PCA was supervized by the APS used significantly more opioid, were more likely to have adjustments made to the PCA dose in response to complaints about inadequate analgesia or side effects, were more likely to be ordered oral opioid analgesia after PCA rather than i.m. opioids, and had significantly fewer side effects.[84] It would seem that the APS used PCA technology in a different manner to non-APS physicians and was more likely to tailor the PCA 'prescription' to suit individual patients.

Inadequate knowledge about the risks of PCA and prescribing by more than one team (e.g. surgical team as well as the APS), have led to inappropriate prescriptions of supplementary opioids (by other routes) and sedative drugs.[2 26 64 94] This may lead to oversedation and respiratory depression.[2 26 94]

The PCA 'prescription'

The PCA prescription includes the parameters that are programmed into the PCA machine, such as bolus dose, lockout interval, dose limits and background infusion, as well as the drugs used. Each may have some effect on the safety and efficacy of PCA.

Bolus dose

The size of the bolus dose (demand dose) can influence the success or otherwise of PCA. The optimal dose will provide good pain relief with minimal side effects.[65] Owen and colleagues[65] studied the effects of a range of doses of morphine—0.5, 1, and 2 mg—and found that most patients who self-administered 0.5 mg were unable to achieve good pain relief, while patients who received 2 mg with every demand had a high incidence of respiratory depression. They concluded, therefore, that 1 mg was the optimal PCA bolus dose for morphine.

Camu and others[7] studied the effects of three different sized bolus doses of fentanyl—20, 40, and 60 µg—and also found that the larger dose was associated with an increased risk of respiratory depression. They concluded that the optimal dose of fentanyl for use in PCA was 40 µg. This is larger than the dose of fentanyl often used in clinical practice. However, in this study, each dose was infused over 10 min (the time of delivery was counted as the lockout period), which could alter the effect of that dose.

In a further attempt to obtain an optimal PCA dose, Love and colleagues[52] designed a hand piece that allowed patients to choose either a 0.5, 1, or 1.5 mg bolus dose of morphine. They compared the efficacy of this system against the usual PCA machine where dose size can only be altered by staff. No differences were found in pain relief, number of demands made, amount of morphine used, patient satisfaction, sleep, or nausea and vomiting. They concluded that the more complex system offered no advantage.

However, as Etches[27] correctly says, PCA is neither a 'one size fits all' or a 'set and forget' therapy. While it is appropriate to commence most patients with a 'standard' size bolus dose, factors such as patient age or a history of prior opioid use must be taken into account. These initial doses may then need to be altered in the light of subsequent pain reports or the onset of any side effects. When this is done, PCA can be better tailored to the individual patient.

The number of demands a patient makes, including the number of 'unsuccessful' demands, is often used as a guide to adjusting the size of the bolus dose. However, there may be a number of reasons for a high demand rate other than pain, including anxiety, patient confusion, or inappropriate patient use (see earlier). In the study by Owen and co-workers[65] mentioned above, patients who received 0.5 mg bolus doses of morphine and complained of poor pain control averaged only four demands each hour even though they could have made a demand every 5 min. That is, patients cannot be relied upon to increase the demand rate enough if the dose is too small.[52] The number of doses successfully delivered each hour could be used as an indication of the need for a change in bolus dose size. If a patient is uncomfortable and already receiving an average of three or more bolus doses an hour, it may be reasonable to consider an increase in dose.[54]

Post-operative PCA opioid requirements in adult patients are known to decrease as patient age increases.[53] In addition, the risk of respiratory depression with PCA use appears to be higher in the elderly patient,[26] and it has, therefore, been suggested that a lower PCA bolus dose should be used.[27 48 53]

The volume of the bolus dose is also a factor that can affect the safety of PCA. If the line into which the PCA opioid is being delivered becomes occluded, it has been recommended that an alarm should sound within three dose activations.[44] In this way, a maximum of three doses only could accumulate in the tubing in the event of an obstruction. In the PCA machine evaluated by Jackson and colleagues[41] the alarm sounded after three presses at 0.5 ml and two presses at 1 ml. It did not do so until 12 presses at 0.1 ml. Low volume bolus doses should, therefore, be avoided.[41 42]

It should be remembered that PCA is essentially a maintenance therapy and, therefore, a patient's pain should be controlled before PCA is started.[27 54]

Lockout interval

The time from the end of delivery of one dose until the machine will respond to another demand is called the lockout interval. As this interval is seen as one of the safety features of a PCA machine, it should ideally take into account the time taken for the patient to feel the full effect of a dose in order to minimize the risk of side effects.[33] However, lockout periods of between 5 and 10 min are commonly prescribed in clinical practice, regardless of the opioid used, even though the full effect of a dose of i.v. morphine may not be seen for 15 min or more.[33 54] If lockout intervals are too long the effectiveness of PCA could be reduced. Shorter lockout periods are more likely to allow the problems of between-patient (8- to 10-fold[53]) and within-patient (in response to differing pain stimuli) variations in opioid requirements to be overcome.[27]

Ginsberg and co-workers[33] studied the effects of varying lockout intervals (7 or 11 min for morphine; 5 or 8 min for fentanyl) and noticed no difference in analgesia, anxiety, or side effects.

Dose limits

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly hourly or 4-hourly limits) can be programmed into most PCA machines. Dose limits for morphine are commonly set at 10 mg in 1 h or 30 mg in 4 h.

For PCA to be used effectively, a wide range of opioid requirements needs to be tolerated. However, there is no reliable method of determining how much opioid a patient will require for analgesia, far less how much will result in dangerous side effects. The signs of excessive morphine dose can present well before these preset limits are reached and, to date, there is no good evidence to show that patients have benefited from their inclusion in PCA prescriptions.[27]

So-called 'safety factors', such as lockout intervals and hourly limits, are no substitution for educated and vigilant monitoring of the patient receiving PCA.

Background infusions

Background (or concurrent continuous) infusions can be delivered by most electronic PCA machines. It had been hoped that the use of an infusion, in addition to bolus doses on demand, would improve analgesia and allow patients to sleep better without waking in severe pain. The drawback is that the opioid will continue to be delivered, regardless of the sedation level of the patient.

Most studies comparing PCA with and without a background infusion have been unable to show that the addition of the infusion improved pain relief[20 55 67] or sleep.[67] However, they also report no difference in the number of demands made,[20 55 67] an increase in the total amount of opioid delivered[20 55 67] and an increase in the incidence of side effects, including respiratory depression, when a background infusion is used. Audits of large numbers of adult patients have also shown that the risk of respiratory depression is increased when a background infusion is prescribed.[29 64 81 80] Programming errors may also increase when background infusions are prescribed.[2 67]

In adults, the routine use of a background infusion is, therefore, not recommended. However, relative safety may be improved if a patient's opioid requirements are already known. A background infusion may be suitable in patients who are opioid-tolerant and in opioid-naive patients who show high opioid requirements or complain of waking in severe pain at night.[27 54]

In children, the use of a background infusion may improve sleep at night,[20] but fails to improve pain relief and may significantly increase the risk of hypoxaemia.[20 57]

PCA devices have been developed that alter the rate of a background infusion according to the demands made by the patient,[40 77] but these devices are not yet in common clinical practice.

Opioid drugs used in PCA

Mather and Woodhouse[55] believe that the success of PCA is independent of the agent used (whether high or low potency, or high or low lipophilicity) and more likely to be affected by the PCA parameters prescribed.

Certainly there is little evidence to suggest major differences in efficacy or side effects between morphine and other commonly used opioids such as pethidine,[85 105] hydromorphone,[72] fentanyl,[105] and oxycodone,[82] although a greater incidence of pruritus may be seen with morphine.[105] Tramadol may have similar analgesic effects to morphine but the incidence of nausea and vomiting may also be greater, while sedation may be decreased.[66]

It should be remembered that these results look across patient populations and it may be that individual responses are highly variable. If drug-related side effects fail to respond to specific treatment, then some patients may experience fewer side effects if a change to another opioid is made.[62]

Any of the opioid-related side effects can occur during PCA therapy but the side effect that causes most concern is respiratory depression. Figures from most audits suggest that the overall incidence in patients using PCA ranges from 0.1 to 0.8%.[2 26 29 64 80 81 101] However, incidences of 1.1 to 3.9% have been found when a concurrent background infusion is used.[29 64 80 81]

Apart from the addition of a background infusion, the risk of respiratory depression with PCA appears to be increased in the elderly patient,[26 80] in patients with OSA,[26 81] when concurrent sedatives or additional opioids are given,[2 26 29] or if patients become hypovolaemic.[26]

Comparison of the risks of respiratory depression with PCA and more conventional opioid analgesic techniques is difficult, as there is a paucity of data relating to the latter methods. The incidence of respiratory depression with conventional methods of opioid administration is probably in the range of 0.2 to 0.9%[5] and an incidence of 1.7% has been reported with continuous i.v. infusions.[80]

Choice of opioid may be more important when there is a need to consider the possible effects of opioid metabolites. In patients with renal failure the use of a drug with no active metabolites, such as fentanyl, might be preferred.[55] Problems resulting from the use of pethidine may occur even in the absence of renal impairment. Norpethidine toxicity, which results in a spectrum of side effects ranging from anxiety and agitation to myoclonic jerks and grand mal seizures (all of which may occur within 24 h of starting therapy) have followed prolonged use and/or high doses of pethidine.[35 56 86]

As the aim of PCA is to allow patients to determine their own opioid requirements, and as the doses required in order to achieve reasonable analgesia are unpredictable and vary enormously between patients, it may be best to avoid the use of pethidine with PCA. If there is no alternative to pethidine, it has been suggested (in patients without renal impairment) that doses be limited to no more than 1000–1200 mg in the first 24 h and that subsequent 24 h doses be lower still.[35 86]

Addition of non-opioid drugs to PCA

Non-opioid analgesic drugs such as ketamine[1] have been added to the opioid in PCA in attempts to improve analgesia and possibly minimize side effects. There is as yet no clear evidence to suggest any benefit from the combination compared with the independent administration of the same drug. As patient opioid requirements are known to vary widely, the amount of adjuvant drug delivered will also vary. Therefore, the practice of combining drugs in the same syringe could lead to an inadequate effect of the adjuvant drug in some patients, and excessive effect in others.

In attempts to minimize nausea and vomiting associated with PCA opioids, antiemetics such as droperidol[30 92 99] and cyclizine[99] have been added to PCA opioid syringes. Again, because of differing patient opioid requirements, the amount of antiemetic delivered could range from ineffective to excessive. Reporting on the results of a systematic search of trials investigating the effects of adding droperidol to PCA morphine, Tramer and colleagues[92] suggest that the total daily dose of droperidol administered should be kept to less than 4 mg in order to minimize the chance of side effects.

The practice of adding antiemetics is still controversial. As adverse effects of droperidol are dose-dependent, the risk of side effects will increase with increased use of PCA.[106] Cost-effectiveness must also be considered, as the routine addition of an antiemetic to PCA opioid means that all patients receive the drugs even when not all patients need them.[106] Tramer and colleagues[92] concluded that if 100 patients are treated in this manner, 30 will benefit. Gan and others[30] compared the addition of droperidol to PCA morphine with droperidol given separately and found both regimens to be equally as effective.

Conclusions

PCA can be a very effective and safe method of pain relief and may allow easier individualization of therapy compared with conventional methods of opioid analgesia. However, it is not a 'one size fits all' or a 'set and forget' therapy and original prescriptions may need to be adjusted if maximal benefit is to be given to all patients. Efficacy and safety will also be increased if attention is paid to the factors outlined above. Thus, the success or otherwise of PCA lies in how well it is used.

This comment applies equally to conventional techniques for opioid administration. Effective pain relief requires flexibility in dose regimens, the ability to deliver the dose to the patient truly 'on demand' (i.e. 'patient-controlled'), regular monitoring of adequacy of analgesia and of any drug-related side effects, and the use of these parameters to individualize treatment. PCA devices really only facilitate this process. Setting aside patient preference and any arguments about the pros and cons of i.m. or s.c. injections, if similar attention can be given to other methods of opioid administration, conventional methods of analgesia could be as effective as PCA in many patients. However, in many busy hospital wards, staff numbers, time, attitudes, and knowledge may serve to limit the efficacy of nurse-administered pain relief. It is, therefore, likely that the popularity of PCA will continue and that PCA will remain a commonly used method of analgesia.

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References

1 Adriaenssens G, Vermeyen KM, Hoffmann VL, Mertens E, Adriaensen HF. Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine. *Br J Anaesth* 1999; **83**: 393–6

2 Ashburn MA, Love G, Pace NL. Respiratory-related critical events with intravenous patient-controlled analgesia. *Clin J Pain* 1994; **10**: 52–6

3 Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. *J Clin Anesth* 1993; **5**: 182–93

4 Ballantyne JC, Carr DB, deFerranti S, *et al.* The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; **86**: 598–612

5 Baxter AD. Respiratory depression with patient-controlled analgesia. *Can J Anaesth* 1994; **41**: 87–90

6 Boldt J, Thaler E, Lehmann A, Papsdorf M, Isgro F. Pain management in cardiac surgery patients: comparison between standard therapy and patient-controlled analgesia regimen. *J Cardiothorac Vasc Anesth* 1998; **12**: 654–8

7 Camu F, Van Aken H, Bovill JG. Postoperative analgesic effects of three demand-dose sizes of fentanyl administered by patient-controlled analgesia. *Anesth Analg* 1998; **87**: 890–5

8 Chan VW, Chung F, McQuestion M, Gomez M. Impact of patient-controlled analgesia on required nursing time and duration of postoperative recovery. *Reg Anesth* 1995; **20**: 506–14

9 Chisakuta AM. Nurse-call button on a patient-controlled analgesia pump? *Anaesthesia* 1993; **48**: 90

10 Choi YK, Brolin RE, Wagner BK, Chou S, Etesham S, Pollak P. Efficacy and safety of patient-controlled analgesia for morbidly obese patients following gastric bypass surgery. *Obes Surg* 2000; **10**: 154–9

11 Choiniere M, Grenier R, Paquette C. Patient-controlled analgesia: a double-blind study in burn patients. *Anaesthesia* 1992; **47**: 467–72

12 Choiniere M, Rittenhouse BE, Perreault S, *et al.* Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. *Anesthesiology* 1998; **89**: 1377–88

13 Christie L, Cranfield KA. A dangerous fault with a PCA pump. *Anaesthesia* 1998; **53**: 827

14 Chumbley GM, Hall GM, Salmon P. Patient-controlled analgesia: an assessment by 200 patients. *Anaesthesia* 1998; **53**: 216–21

15 Coleman SA, Booker-Milburn J. Audit of postoperative pain control. Influence of a dedicated acute pain nurse. *Anaesthesia* 1996; **51**: 1093–6

16 Colwell CW Jr, Morris BA. Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopaedic procedure. *J Bone Joint Surg Am* 1995; **77**: 726–33

17 Costigan SN. Malfunction of a disposable PCA device. *Anaesthesia* 1994; **49**: 352

18 Dawson L, Brockbank K, Carr EC, Barrett RF. Improving patients' postoperative sleep: a randomized control study comparing subcutaneous with intravenous patient-controlled analgesia. *J Adv Nurs* 1999; **30**: 875–81

19 D'Haese J, Vanlersberghe C, Umbrain V, Camu F. Pharmaco-economic evaluation of a disposable patient-controlled analgesia device and intramuscular analgesia in surgical patients. *Eur J Anaesthesiol* 1998; **15**: 297–303

20 Doyle E, Robinson D, Morton NS. Comparison of patient-controlled analgesia with and without a background infusion after lower abdominal surgery in children. *Br J Anaesth* 1993; **71**: 670–3

21 Dunbar PJ, Buckley P, Gavrin JR, Sanders JE, Chapman CR. Use of patient-controlled analgesia for pain control for children receiving bone marrow transplant. *J Pain Symptom Manage* 1995; **10**: 604–11

22 ECRI. Improper cassette attachment allows gravity free-flow from SIMS-Deltec CADD-series pumps. *Health Devices* 1995; **24**: 84–6

23 ECRI. Overinfusion caused by gravity free-flow from a damaged prefilled glass syringe. *Health Devices* 1996; **25**: 476–7

24 ECRI. Abbott PCA Plus II patient-controlled analgesic pumps prone to misprogramming resulting in narcotic overinfusions. *Health Devices* 1997; **26**: 389–91

25 Egbert AM, Parks LH, Short LM, Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med* 1990; **150**: 1897–903

26 Etches RC. Respiratory depression associated with patient-controlled analgesia: a review of eight cases. *Can J Anaesth* 1994; **41**: 125–32

27 Etches RC. Patient-controlled analgesia. *Surg Clin North Am* 1999; **79**: 297–312

28 Finger MJ, McLeod DG. Postoperative myocardial infarction after radical cystoprostatectomy masked by patient-controlled analgesia. *Urology* 1995; **45**: 155–7

29 Fleming BM, Coombs DW. A survey of complications documented in a quality-control analysis of patient-controlled analgesia in the postoperative patient. *J Pain Symptom Manage* 1992; **7**: 463–9

30 Gan TJ, Alexander R, Fennelly M, Rubin AP. Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. *Anesth Analg* 1995; **80**: 81–5

31 Geller RJ. Meperidine in patient-controlled analgesia: a near-fatal mishap. *Anesth Analg* 1993; **76**: 655–7

32 Gil KM, Ginsberg B, Muir M, Sykes D, Williams DA. Patient-controlled analgesia in postoperative pain: the relation of psychological factors to pain and analgesic use. *Clin J Pain* 1990; **6**: 137–42

33 Ginsberg B, Gil KM, Muir M, Sullivan F, Williams DA, Glass PS. The influence of lockout intervals and drug selection on patient-controlled analgesia following gynecological surgery. *Pain* 1995; **62**: 95–100

34 Gust R, Pecher S, Gust A, Hoffmann V, Bohrer H, Martin E. Effect of patient-controlled analgesia on pulmonary complications after coronary artery bypass grafting. *Crit Care Med* 1999; **27**: 2218–23

35 Hagmeyer KO, Mauro LS, Mauro VF. Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27**: 29–32

36 Harmer M. Overdosage during patient controlled analgesia. Follow manufacturers' instructions. *BMJ* 1994; **309**: 1583

37 Harrington P, Bunola J, Jennings AJ, Bush DJ, Smith RM. Acute compartment syndrome masked by intravenous morphine from a patient-controlled analgesia pump. *Injury* 2000; **31**: 387–9

38 Heath ML. Safety of patient controlled analgesia. *Anaesthesia* 1995; **50**: 573

39 Hodsman NB, Kenny GN, McArdle CS. Patient controlled analgesia and urinary retention. *Br J Surg* 1988; **75**: 212

40 Irwin MG, Jones RD, Visram AR, Kenny GN. Patient-controlled alfentanil. Target-controlled infusion for postoperative analgesia. *Anaesthesia* 1996; **51**: 427–30

41 Jackson IJ, Semple P, Stevens JD. Evaluation of the Graseby

PCAS. A clinical and laboratory study. *Anaesthesia* 1991; **46**: 482–5

42 Jacox A, Carr DB, Mahrenholz DM, Ferrell BM. Cost considerations in patient-controlled analgesia. *Pharmacoeconomics* 1997; **12**: 109–20

43 Jamison RN, Taft K, O'Hara JP, Ferrante FM. Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. *Anesth Analg* 1993; **77**: 121–5

44 Kluger MT, Owen H. Antireflux valves in patient-controlled analgesia. *Anaesthesia* 1990; **45**: 1057–61

45 Kluger MT, Owen H. Patients' expectations of patient-controlled analgesia. *Anaesthesia* 1990; **45**: 1072–4

46 Kwan A. Overdose of morphine during PCA. *Anaesthesia* 1995; **50**: 919

47 Kyzer S, Ramadan E, Gersch M, Chaimoff C. Patient-controlled analgesia following vertical gastroplasty: a comparison with intramuscular narcotics. *Obes Surg* 1995; **5**: 18–21

48 Lavand'Homme P, De Kock M. Practical guidelines on the postoperative use of patient-controlled analgesia in the elderly. *Drugs Aging* 1998; **13**: 9–16

49 Leeson-Payne CG, Towell T. Magnetic mayhem. *Anaesthesia* 1996; **51**: 1081–2

50 Levin A, Klein SL, Brolin RE, Pitchford DE. Patient-controlled analgesia for morbidly obese patients: an effective modality if used correctly. *Anesthesiology* 1992; **76**: 857–8

51 Lin L, Isla R, Doniz K, Harkness H, Vicente KJ, Doyle DJ. Applying human factors to the design of medical equipment: patient-controlled analgesia. *J Clin Monit Comput* 1998; **14**: 253–63

52 Love DR, Owen H, Ilsley AH, Plummer JL, Hawkins RM, Morrison A. A comparison of variable-dose patient-controlled analgesia with fixed-dose patient-controlled analgesia. *Anesth Analg* 1996; **83**: 1060–4

53 Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. *Pain* 1996; **64**: 357–64

54 Macintyre PE, Ready LB. *Acute Pain Management – A Practical Guide*, 2nd edn. London: WB Saunders, 2001

55 Mather LE, Woodhouse A. Pharmacokinetics of opioids in the context of patient controlled analgesia. *Pain Rev* 1997; **4**: 20–32

56 McHugh GJ. Norpethidine accumulation and generalized seizure during pethidine patient-controlled analgesia. *Anaesth Intensive Care* 1999; **27**: 289–91

57 McNeely JK, Trentadue NC. Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. *J Pain Symptom Manage* 1997; **13**: 268–73

58 Meyer GS, Eagle KA. Patient-controlled analgesia masking pulmonary embolus in a postoperative patient. *Crit Care Med* 1992; **20**: 1619–21

59 Mulligan MA. The innovative use of a patient-controlled analgesia pump for the management of cardiac angina. *J Palliat Care* 1998; **14**: 47–9

60 Munro AJ, Long GT, Sleigh JW. Nurse-administered subcutaneous morphine is a satisfactory alternative to intravenous patient-controlled analgesia morphine after cardiac surgery. *Anesth Analg* 1998; **87**: 11–5

61 Myles PS, Buckland MR, Cannon GB, Bujor MA, Langley M, Breaden A, Salamonsen RF, Davis BB. Comparison of patient-controlled analgesia and nurse-controlled infusion analgesia after cardiac surgery. *Anaesth Intensive Care* 1994; **22**: 672–8

62 NHMRC. Acute pain management: scientific evidence. Canberra: National Health and Medical Research Council of Australia; 1999 (http://www.nhmrc.health.gov.au/publicat/pdf/cp57.pdf)

63 Notcutt WG, Knowles P, Kaldas R. Overdose of opioid from patient-controlled analgesia pumps. *Br J Anaesth* 1992; **69**: 95–7

64 Notcutt WG, Morgan RJ. Introducing patient-controlled analgesia for postoperative pain control into a district general hospital. *Anaesthesia* 1990; **45**: 401–6

65 Owen H, Plummer JL, Armstrong I, Mather LE, Cousins MJ. Variables of patient-controlled analgesia. 1. Bolus size. *Anaesthesia* 1989; **44**: 7–10

66 Pang WW, Mok MS, Lin CH, Yang TF, Huang MH. Comparison of patient-controlled analgesia (PCA) with tramadol or morphine. *Can J Anaesth* 1999; **46**: 1030–5

67 Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. *Anesthesiology* 1992; **76**: 362–7

68 Paterson JG. Intravenous obstruction and PCA machines. *Can J Anaesth* 1998; **45**: 284

69 Pellino TA, Ward SE. Perceived control mediates the relationship between pain severity and patient satisfaction. *J Pain Symptom Manage* 1998; **15**: 110–6

70 Perry F, Parker RK, White PF, Clifford PA. Role of psychological factors in postoperative pain control and recovery with patient-controlled analgesia [see comments]. *Clin J Pain* 1994; **10**: 57–63; discussion 82–5

71 Pettersson PH, Lindskog EA, Owall A. Patient-controlled versus nurse-controlled pain treatment after coronary artery bypass surgery. *Acta Anaesthesiol Scand* 2000; **44**: 43–7

72 Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW, Ching JM. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 1996; **82**: 1043–8

73 Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. *Pain* 1995; **61**: 195–201

74 Richtsmeier AJ Jr, Barnes SD, Barkin RL. Ventilatory arrest with morphine patient-controlled analgesia in a child with renal failure. *Am J Ther* 1997; **4**: 255–7

75 Robinson SL, Rowbotham DJ, Mushambi M. Electronic and disposable patient-controlled analgesia systems. A comparison of the Graseby and Baxter systems after major gynaecological surgery. *Anaesthesia* 1992; **47**: 161–3

76 Rowbotham DJ, Wyld R, Nimmo WS. A disposable device for patient-controlled analgesia with fentanyl. *Anaesthesia* 1989; **44**: 922–4

77 Rudolph H, Cade JF, Morley PT, Packer JS, Lee B. Smart technology improves patient-controlled analgesia: a preliminary report. *Anesth Analg* 1999; **89**: 1226–32

78 Sanchez-Guijo JJ, Benavente MA, Crespo A. Failure of a patient-controlled analgesia pump in a hyperbaric environment. *Anesthesiology* 1999; **91**: 1540–2

79 Schelling G, Weber W, Mendl G, Braun H, Cullmann H. Patient controlled analgesia for shock wave lithotripsy: the effect of self-administered alfentanil on pain intensity and drug requirement. *J Urol* 1996; **155**: 43–7

80 Schug SA, Torrie JJ. Safety assessment of postoperative pain management by an acute pain service. *Pain* 1993; **55**: 387–91

81 Sidebotham D, Dijkhuizen MR, Schug SA. The safety and utilization of patient-controlled analgesia. *J Pain Symptom Manage* 1997; **14**: 202–9

82 Silvasti M, Rosenberg P, Seppala T, Svartling N, Pitkanen M. Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. *Acta Anaesthesiol Scand* 1998; **42**: 576–80

83 Simes D, Power L, Priestley G. Respiratory arrest with patient-controlled analgesia [see comments]. *Anaesth Intensive Care* 1995; **23**: 119–20

84 Stacey BR, Rudy TE, Nelhaus D. Management of patient-controlled analgesia: a comparison of primary surgeons and a dedicated pain service. *Anesth Analg* 1997; **85**: 130–4

85 Stanley G, Appadu B, Mead M, Rowbotham DJ. Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. *Br J Anaesth* 1996; **76**: 484–6

86 Stone PA, Macintyre PE, Jarvis DA. Norpethidine toxicity and patient controlled analgesia. *Br J Anaesth* 1993; **71**: 738–40

87 Striebel HW, Scheitza W, Philippi W, Behrens U, Toussaint S. Quantifying oral analgesic consumption using a novel method and comparison with patient-controlled intravenous analgesic consumption. *Anesth Analg* 1998; **86**: 1051–3

88 Taylor NM, Hall GM, Salmon P. Patients' experiences of patient-controlled analgesia. *Anaesthesia* 1996; **51**: 525–8

89 Thomas DW, Owen H. Patient-controlled analgesia–the need for caution. A case report and review of adverse incidents. *Anaesthesia* 1988; **43**: 770–2

90 Thomas V, Heath M, Rose D, Flory P. Psychological characteristics and the effectiveness of patient-controlled analgesia. *Br J Anaesth* 1995; **74**: 271–6

91 Toussaint S, Maidl J, Schwagmeier R, Striebel HW. Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anaesth* 2000; **47**: 299–302

92 Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review [see comments]. *Anesth Analg* 1999; **88**: 1354–61

93 Tsang J, Brush B. Patient-controlled analgesia in postoperative cardiac surgery. *Anaesth Intensive Care* 1999; **27**: 464–70

94 Tsui SL, Irwin MG, Wong CM, *et al.* An audit of the safety of an acute pain service. *Anaesthesia* 1997; **52**: 1042–7

95 Urquhart ML, Klapp K, White PF. Patient-controlled analgesia: a comparison of intravenous versus subcutaneous hydromorphone. *Anesthesiology* 1988; **69**: 428–32

96 VanDercar DH, Martinez AP, De Lisser EA. Sleep apnea syndromes: a potential contraindication for patient-controlled analgesia. *Anesthesiology* 1991; **74**: 623–4

97 Vanier MC, Labrecque G, Lepage-Savary D, Poulin E, Provencher L, Lamontagne C. Comparison of hydromorphone continuous subcutaneous infusion and basal rate subcutaneous infusion plus PCA in cancer pain: a pilot study. *Pain* 1993; **53**: 27–32

98 Vijay V. The anaesthetist's role in acute sickle cell crisis. *Br J Anaesth* 1998; **80**: 820–8

99 Walder AD, Aitkenhead AR. A comparison of droperidol and cyclizine in the prevention of postoperative nausea and vomiting associated with patient-controlled analgesia. *Anaesthesia* 1995; **50**: 654–6

100 Watson TJ. *Sociology, Work and Industry*. London: Routledge & Kegan Paul Ltd; 1987

101 Wheatley RG, Madej TH, Jackson IJ, Hunter D. The first year's experience of an acute pain service. *Br J Anaesth* 1991; **67**: 353–9

102 Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* 2001; **87**: 47–61

103 White PF. Mishaps with patient-controlled analgesia. *Anesthesiology* 1987; **66**: 81–3

104 White PF. Subcutaneous-PCA: an alternative to IV-PCA for postoperative pain management. *Clin J Pain* 1990; **6**: 297–300

105 Woodhouse A, Hobbes AF, Mather LE, Gibson M. A comparison of morphine, pethidine and fentanyl in the postsurgical patient-controlled analgesia environment. *Pain* 1996; **64**: 115–21

106 Woodhouse A, Mather LE. Nausea and vomiting in the postoperative patient-controlled analgesia environment. *Anaesthesia* 1997; **52**: 770–5

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Safety and efficacy of postoperative epidural analgesia

R. G. Wheatley[1]* , S. A. Schug [2] and D. Watson[2]

[1]Acute Pain Management Unit, York District Hospital, York YO3 7HE, UK. [2]Section of Anaesthetics, Department of Pharmacology, University of Auckland, PO Box 92019, Auckland, New Zealand
**Corresponding author: The Old Barn, Main Street, Shipton, York YO30 1AA, UK*

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Effective analgesia for postoperative pain relief after major surgery has been a practical proposition with epidural administration of local anaesthetic (LA) and opioid drugs since the early 1980s. Although epidural administration is perceived by 80% of UK anaesthetists as the ideal analgesic technique for upper abdominal surgery,[34] there are many patients undergoing major surgery who do not receive this form of analgesia. In a recent survey of UK practice, only 15% of patients undergoing abdominal surgery had epidural analgesia in the 12 hospitals sampled.[31] The main factor which has limited the use of epidural analgesia has been the difficulty in making a reasonable risk/benefit analysis about the technique, which has resulted in clinicians constantly asking whether epidurals are effective for postoperative pain relief and whether the technique is safe.

This review considers the efficacy and safety of epidural analgesia in patients recovering from major surgery and is based on a computerized search of the literature from 1976 to 2000 (EMBASE/Medline). The final section will deal with the organizational issues which need to be considered to maximize efficacy and safety and is based on the authors' joint experience of supervising acute pain services (APS) in New Zealand and the UK; these services have been responsible for pain relief in over 20 000 patients nursed on general postoperative wards.

Efficacy

Efficacy has been defined as 'the ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances'. It is important to bear this definition in mind as the published results on efficacy are usually based on expert practice in optimal conditions. The difficulties in making this transition from the controlled setting of a clinical trial to routine clinical practice have been highlighted by the results of recently published audits,[4] [124] which have demonstrated a failure rate of 30–50% for epidural analgesia.

The ideal epidural analgesic technique for major surgery would provide effective pain relief with minimal side effects and high levels of patient satisfaction. It would also obtund central sensitization and pain-induced organ dysfunction, leading to improved outcome. This topic is covered in the accompanying review in this issue on postoperative pain relief and surgical outcome[83]. It is self-evident that the primary measure of efficacy of any analgesic regimen is pain relief. However, pain is a complex, subjective experience which has proved difficult to measure in a reproducible way. Early studies of postoperative analgesia relied on measurement of pain scores at rest and surrogate measures, such as respiratory spirometry. Reliance on measuring pain scores at rest resulted in failure to identify those techniques which allowed patients to mobilize and cough effectively, i.e. techniques that provided dynamic pain relief.[42] Total dynamic pain relief, i.e. complete absence of pain on moving and coughing after major upper abdominal surgery, can be produced in the intensive care environment by the use of large doses of opioid and LA drugs. This is an unrealistic aspiration for a ward-based analgesic technique, as high doses of these drugs are associated with an unacceptable incidence of hypotension and respiratory depression. A more realistic approach is to measure pain on movement or coughing and to aim for a patient who can mobilize, take deep breaths and cough effectively and who scores 3 or less out of 10 on a visual analogue or numerical rating scale measured on movement.[133] Although many studies have used spirometric assessment as an outcome measure, a recent meta-analysis cast doubt on the validity of using these techniques as a surrogate measure of the efficacy of epidural analgesia.[9]

The difficulty with interpreting the available data on efficacy is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space before or after surgical incisions for a wide variety of operations. In this section of the review we consider the evidence from randomized controlled trials (RCTs) in which dynamic pain relief was an outcome measure, in order to assess the factors which modify the effectiveness of

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Table 1 RCTs comparing lipophilic opioid epidural infusions with intravenous or patient-controlled intravenous opioids with dynamic pain relief as an outcome measure. NS difference=no significant difference; PCEA=patient controlled epidural anaesthesia

Reference	No. of patients	Epidural regimen	Site of insertion	Type of surgery	Comparator	Dynamic pain relief compared with control group	Comments
99	20	Fentanyl infusion 100 $\mu g\ h^{-1}$	Lumbar	Knee	i.v. fentanyl infusion100 $\mu g\ h^{-1}$	NS difference	NS difference in plasma concentrations
3	66	Fentanyl infusion 1 $\mu g\ kg^{-1}\ h^{-1}$	Lumbar	Lower abdominal	i.v. PCA morphine	Epidural more effective	
13	36	Fentanyl infusion 50 $\mu g\ h^{-1}$	Thoracic	Thoracic	i.v. PCA morphine	Epidural more effective	
36	40	Fentanyl PCEA 20 µg bolus	Lumbar	Lower abdominal	I.v. PCA fentanyl 20 µg bolus	Epidural more effective at 8–12 h	Reduced fentanyl consumption in the epidural group
28	32	Alfentanil PCEA 250 µg bolus	Thoracic	Major abdominal	i.v. alfentanil PCA 250 µg bolus	NS difference	Reduced alfentanil consumption in the epidural group
107	50	Sufentanil infusion 0.2 $\mu g\ kg^{-1}\ h^{-1}$	Lumbar	Major abdominal	i.v. sufentanil 0.2 $\mu g\ h^{-1}$	NS difference	NS difference in opioid dose
38	84	Fentanyl PCEA 20 µg bolus	Lumbar	Lower abdominal	I.v. PCA morphine	Epidural more effective for 21 h	

epidural analgesia such as the choice of drugs, the site of epidural insertion in relation to the surgical incision and the timing and method of drug delivery.

Choice of drug

Local anaesthetic

Epidural LA drugs administered alone have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block[110] and the unacceptable incidence of motor blockade and hypotension. In a study of patients undergoing thoracic surgery, despite the infusion of bupivacaine 37.5–50 mg h^{-1} via a thoracic epidural, 30% of patients required opioid supplementation for inadequate analgesia and 80% had significant hypotension.[33] Similar results were also found when bupivacaine 24–45 mg h^{-1} or ropivacaine 10–30 mg h^{-1} was infused epidurally after upper[131 141] and lower[53 108] abdominal surgery. In an opioid-free postoperative analgesic regimen, infusion rates of bupivacaine 10–12.5 mg h^{-1} supplemented by systemic non-steroidal anti-inflammatory drugs were found to be ineffective in lower abdominal surgery.[25]

Opioids

The use of epidural analgesia for pain relief was revolutionized by the use of epidural opioids after the discovery of opioid receptors in the dorsal horn of the spinal cord. Opioids have both presynaptic and postsynaptic effects in the dorsal horn and affect the modulation of nociceptive input but do not cause motor or sympathetic blockade.

Despite the initial enthusiasm for epidural opioids, with their promise of profound, long-lasting analgesia with minimal side-effects, there is still considerable debate about their place in postoperative pain management.[29 44]

Opioid-based techniques have been used widely in the USA and Australia and are usually based on bolus administration of drugs such as morphine, diamorphine and pethidine or the continuous infusion of lipophilic opioids such as fentanyl or sufentanil.

Although bolus epidural opioids may produce longer-lasting analgesia with smaller doses than intermittent i.m. opioids,[29] there is less convincing evidence that they improve the quality of analgesia when the technique is compared to i.v. patient-controlled anaesthesia (PCA).[60]

The RCTs of continuous infusions of lipophilic opioids compared with i.v. or patient-controlled i.v. opioids in which pain on coughing or movement was assessed are shown in Table 1.

The evidence for a spinal rather than a systemic action of fentanyl is conflicting. Although significant differences in efficacy were not demonstrated when fentanyl or sufentanil were administered epidurally or i.v. after knee[99] or major abdominal[28 107] surgery, epidural fentanyl produced more effective dynamic pain relief than i.v. PCA morphine or fentanyl in lower abdominal[3 36 38] and thoracic[13] surgery. In the majority of studies in which plasma concentrations have been measured,[11 99 137] there was no significant difference in plasma concentrations between the two routes of administration. Furthermore, plasma concentrations of fentanyl were usually above the minimum effective analgesic concentration of 0.23–1.18 (mean 0.63) ng ml^{-1} for i.v. fentanyl.[62]

On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route appear to be marginal, or unproven in the case of upper abdominal surgery, and in many situations will not outweigh the risks of the more invasive route of administration.

Opioid–local anaesthetic combinations

Epidural infusions of LA–opioid combinations are the most commonly used epidural technique in the UK[34] and Australia,[35] being used by 97% of anaesthetists who use the technique. Their use is based on the clinical observation that the combination of LA and opioid drugs limits the regression of the sensory block seen with LAs alone[65] and improves the quality of dynamic pain relief.[42] However, there are major regional and national differences in the choice of opioid and LA drugs used for postoperative epidural analgesia. In a UK survey, 40% of anaesthetic departments used diamorphine and 51% used fentanyl in combination with LA drugs.[129]

The RCTs comparing LA–opioid combinations and LA or opioids alone with dynamic pain relief as an outcome measure are shown in Table 2.

The majority of studies show that the use of a mixture of LA and opioid is associated with significantly better dynamic pain relief after lower or upper abdominal,[39,42,101,119,145,146,168] orthopaedic[79,87] and thoracic[95,115,168] surgery than the components of the mixture infused alone.

However, in a within-patient crossover study, Torda and colleagues could not demonstrate any difference in efficacy between bolus doses of fentanyl 50 µg, bupivacaine 50 mg or a mixture of both.[157] Similarly, Mahon and colleagues were unable to demonstrate any improvement in efficacy by adding 0.1–0.2% bupivacaine to fentanyl 10 µg ml^{-1} after the first 2 h after thoracotomy.[103]

Epidural analgesia with LA–opioid combinations has been shown to be significantly better than i.v. PCA morphine in providing dynamic pain relief after major abdominal surgery[18,97,104,113] (Table 3).

Is there an optimal combination of opioid and LA for epidural analgesia? Despite differences in epidural to systemic potency between different opioid drugs, there are no RCTs, with dynamic pain relief as an outcome measure, which compare the efficacy of different epidural LA–opioid combinations. However, it is clear that the co-administration of LA with opioid significantly reduces the opioid requirement of all opioids studied. Many of the early studies used a fentanyl concentration of 10 µg ml^{-1} on the basis of a dose-finding study of epidural fentanyl used alone.[165] In a subsequent dose-finding study, in which fentanyl was combined with 0.125% levobupivacaine, an optimal concentration of 4 µg ml^{-1} was recommended.[145] Similarly, reduced concentrations of less lipophilic opioids, such as 50 µg ml^{-1} of morphine[39,42] and diamorphine,[101] have been shown to be effective.

The optimal dose of the LA component of the epidural mixture is becoming clearer. In two postoperative studies in which pain relief on movement[37,52] was not significantly better in the combination group, the concentration of bupivacaine used was 0.1% or less and it was delivered as patient-controlled epidural anaesthesia (PCEA) without a background infusion. A dose of 4–12 mg h^{-1} of bupivacaine, when combined with morphine 50 µg ml^{-1},[42] diamorphine 80 µg ml^{-1},[101] fentanyl 10 µg ml^{-1},[119] sufentanil 1 µg ml^{-1},[168] and administered via a thoracic epidural catheter, has been shown to provide effective dynamic pain relief. The addition of opioid, therefore, significantly reduces the hourly requirement of bupivacaine from 25–45 mg h^{-1} when used alone.[33,108,131]

In a recent study, in which a direct search procedure was used to determine the optimal combinations of thoracic epidural bupivacaine and fentanyl after major abdominal surgery, the two most effective regimens were bupivacaine 8 mg h^{-1} and fentanyl 30 µg h^{-1} or bupivacaine 13 mg h^{-1} and fentanyl 25 µg h^{-1}; both infused at 9 ml h^{-1}.[40]

Although the doses of LA are small, it is likely that the newer LA drugs, levobupivacaine and ropivacaine, will be used increasingly because of their improved safety margin and, in the case of ropivacaine, the potential advantage of less motor blockade. Although this latter advantage appears to be relevant at the higher concentrations used for intraoperative analgesia, the differences between the drugs are less marked at the dilute concentrations used for postoperative analgesia. In a study after major abdominal surgery, 0.2% ropivacaine was not significantly different, in terms of analgesia or motor blockade, from 0.125% bupivacaine when both were combined with fentanyl 2 µg ml^{-1}.[14]

Site of insertion

A meta-analysis of studies comparing the thoracic or lumbar approaches to the epidural space for opioids alone failed to demonstrate any significant improvement in analgesia when the thoracic approach was used.[9]

There are no RCTs comparing LA–opioid combinations administered via the thoracic and lumbar approaches. Nevertheless, the use of the thoracic rather than the lumbar approach to the epidural space has been one of the major changes in anaesthetic practice over the last 20 yr and has been used in the majority of studies that have demonstrated improved dynamic pain relief.[39,42,95,97,101,104,113,115,119,145,146,168] This technique has a number of potential benefits when used for the administration of LA–opioid mixtures. The thoracic approach facilitates the incision-congruent administration of lipophilic opioids in small doses and minimizes motor and sympathetic blockade of the lower

Table 2 RCTs, comparing LA–opioid combinations with epidural opioids or local anaesthetic alone, with dynamic pain relief as an outcome measure. NS difference = no significant difference

Reference	No. of patients	Epidural regimen	Type of surgery/site of epidural	Comparator	Dynamic pain relief compared with control group	Comments
146	22	Morphine 500 μg h^{-1} 0.5% bupivacaine 25 mg h^{-1}	Upper abdominal/thoracic	0.5% Bupivacaine 25 mg h^{-1}	Combination more effective	2 patients withdrawn because of hypotension or respiratory depression
42	24	Morphine 200 μg h^{-1} 0.25% bupivacaine 10 mg h^{-1}	Major abdominal/thoracic	Morphine 200 μg h^{-1}	Combination more effective	
39	64	Morphine 200 μg h^{-1} 0.25% levobupivacaine 10 mg h^{-1}	Major abdominal/thoracic	Morphine 200 μg h^{-1}	Combination more effective for the first 8 h	Less supplementary analgesia required
101	40	Diamorphine 250–600 μg h^{-1} 0.167% bupivacaine 5–12 mg h^{-1}	Upper abdominal/thoracic	Diamorphine 250–600 μg h^{-1}	Combination more effective	
53	66	Pethidine 1 mg ml^{-1} 0.1% bupivacaine PCEA: no background 5 ml/15 min	Thoracic/thoracic	Pethidine	NS difference	NS difference in drug consumption
119	90	Fentanyl 40 μg h^{-1} 0.1% bupivacaine 4 mg h^{-1}	Major abdominal/thoracic	Fentanyl 40 μg h^{-1}	Combination more effective for the first 24 h	
157	24	Fentanyl 50 μg + bupivacaine 12.5 or 25 mg bolus doses	Major abdominal surgery/thoracic	Fentanyl 50 μg	NS difference	
95	24	Fentanyl PCEA 0.01–0.1% bupivacaine 10 ml h^{-1}	Thoracic	Fentanyl PCEA	Combination more effective	Optimal bupivacaine dose 5 mg h^{-1}
37	60	Fentanyl 2 μg ml^{-1} bupivacaine 0.05% PCEA: no background 5 ml/10 min	Lower abdominal/lumbar	Fentanyl 4 μg ml^{-1} or 0.15% bupivacaine PCEA	NS difference	Significantly reduced fentanyl or bupivacaine doses when combination used
103	106	Fentanyl 50–100 μg h^{-1} 0.1–0.2% bupivacaine 5–20 mg h^{-1}	Thoracic/thoracic	Fentanyl 50–100 μg h^{-1}	NS difference after the first 2 h	
88	68	Fentanyl 4 μg ml^{-1} levobupivacaine 0.125% PCEA 4 ml h^{-1} + 2 ml/10 min bolus	Arthroplasty/lumbar	Fentanyl 4 μg ml^{-1} or 0.125% levobupivacaine PCEA	Combination more effective	NS difference in opioid doses
145	259	Fentanyl 1–4 μg ml^{-1} 0.2% ropivacaine PCEA 8 ml h^{-1} + 4 ml/30 min bolus	Major abdominal/thoracic	Ropivacaine 0.2%	Combination more effective	Optimal fentanyl dose 4 μg ml^{-1}
115	50	Sufentanil 0.8 μg ml^{-1} 0.125% bupivacaine 6–12 mg h^{-1}	Thoracic/thoracic	Sufentanil 0.8 μg ml^{-1} or 0.125% bupivacaine 5–10 ml h^{-1}	Combination more effective	0.125% bupivacaine ineffective
168	100	Sufentanil 1 μg ml^{-1} 0.17% bupivacaine PCEA 5 ml h^{-1} + 2 ml/20 min bolus	Thoracic abdominal	0.17% Bupivacaine	Combination more effective	Less supplementary analgesia required
79	30	Sufentanil 5–9 μg h^{-1} 0.1% ropivacaine 5–9 mg h^{-1}	Orthopaedic/ lumbar	0.1% Ropivacaine	Combination more effective	Less supplementary analgesia required

Table 3 RCTs comparing epidural LA- opioid combinations with i.v. PCA with dynamic pain relief as an outcome measure

Reference	No. of patients	Epidural regimen	Site of insertion	Type of surgery	Post-operative analgesia	Dynamic pain relief
97	54	Morphine 300 μg h^{-1} 0.1% bupivacaine 10 mg h^{-1}	Thoracic	Major abdominal	I.v. PCA morphine	Better in the epidural group
18	40	Morphine 400 μg h^{-1} 0.125% bupivacaine 6 mg h^{-1}	Lumbar	Aortic	I.v. PCA morphine	Better in the epidural group
113	60	Morphine 250 μg h^{-1} 0.125% bupivacaine 12.5 mg h^{-1}	Thoracic	Major abdominal	I.v. PCA morphine	Better in the epidural group
104	70	PCEA sufentanil 0.5μg ml^{-1} + 0.125% bupivacaine 3–5 ml h^{-1}	Thoracic	Major abdominal surgery	I.v. PCA morphine	Better in the epidural group

limbs. Although initially seen as a disadvantage because of the attendant hypotension, the importance of a controllable degree of sympathetic blockade in the attenuation of the adverse adrenergic effects on the cardiovascular and gastrointestinal systems is now being realized.[128]

Pre- or post-incisional epidural analgesia

In order to see a pre-emptive effect with an analgesic intervention, it is necessary to provide good analgesia with inhibition of central sensitization extending into the postoperative period.[169] This may explain the lack of pre-emptive effect when an epidural is given before or after surgical incision and analgesia is provided in the postoperative period by i.v. PCA morphine[51 126] (Table 4).

However, no significant difference in dynamic pain relief was seen when bupivacaine and morphine were given before and after incision and continued into the post-operative period[41] or when bupivacaine alone was given followed by PCEA with fentanyl and bupivacaine.[2] Two recent studies have demonstrated a pre-emptive effect. Using a mixture of ketamine, bupivacaine and morphine, Wu and colleagues demonstrated a statistically significant improvement in analgesia in the pre-incisional group after upper abdominal surgery during the first postoperative day.[171] However, the differences in clinical terms were marginal as patients in both groups had good dynamic pain relief. Patients recovering from radical prostatectomy, all of whom had an aggressive postoperative epidural analgesic regimen, had significantly less pain in hospital and 9.5 weeks later if they had had epidural fentanyl or bupivacaine administered before surgical incision.[61] Although this is one of the few studies demonstrating a clinically significant pre-emptive effect, its conclusions are limited by the fact that pain scores were measured at rest.

Method of drug delivery

Bolus versus infusion

postoperative epidural analgesia is usually administered via a continuous infusion to maintain a level of analgesia and to minimize the cardiovascular and respiratory effects of bolus doses of LA and opioid respectively. Intermittent bolus dosing of LA alone has been shown to minimize block regression and marginally improve analgesia compared with a continuous infusion of the same hourly dose in patients undergoing lower abdominal surgery.[48] However, there was no difference in pain scores on coughing between the two groups, and this technique has not been studied in patients receiving epidural LA–opioid combinations for upper abdominal surgery.

PCEA with or without a background infusion

Allowing patients to have control of their analgesia has become an important principle in acute pain management. Although the role and optimal regimen of PCEA after major surgery have not yet been fully clarified, the technique has the practical safety advantage of permitting bolus doses which do not require to be mixed on the ward. The importance of a background infusion when using an LA–opioid combination was emphasized in a recent study in patients recovering from gastrectomy when PCEA alone was shown to be less effective in reducing pain on coughing than PCEA with a background infusion.[86]

Choice of adjuvants

In addition to LA agents and opioids, a number of agents have been used as adjuvants to improve the efficacy of epidural analgesia. These include ketamine [antagonist of NMDA (*N*-methyl-D-aspartate)], midazolam [agonist of GABA (γ-aminobutyric acid)], clonidine (α2 agonist) and adrenaline.

The results of RCTs of adjuvant agents added to LA–opioid combinations are shown in Table 5.

Table 4 RCTs of pre- versus post-incisional administration of epidural analgesia with dynamic pain relief as an outcome measure. NS difference = no significant difference

Reference	No. of patients	Epidural regimen	Site of insertion	Type of surgery	Postoperative analgesia	Dynamic pain relief
51	40	0.5% bupivacaine 20 ml	Lumbar	Lower abdominal	PCA i.v. morphine	NS difference
126	25	0.5% bupivacaine 15 ml + fentanyl 50 μg	Lumbar	Lower abdominal	PCA i.v. morphine	NS difference
141	32	0.75% bupivacaine 7 ml + morphine 2 mg	Thoracic	Major abdominal	Epidural morphine + bupivacaine	NS difference
2	45	bupivacaine 8 ml + epinephrine	Thoracic	Thoracic	PCEA fentanyl + bupivacaine + epinephrine	NS difference
171	60	Ketamine + morphine + bupivacaine	Thoracic	Upper abdominal surgery	Ketamine + morphine + bupivacaine twice per day	Significantly better in the pre-incisional group

Table 5 RCTs of adjuvant therapy plus LA–opioid combinations with dynamic pain relief as an outcome measure

Reference	No. of patients	Epidural regimen	Site of insertion	Type of surgery	Adjuvant	Dynamic pain relief
30	91	PCEA morphine 20 μg ml^{-1} + 0.08% bupivacaine + epinephrine 4 μg ml^{-1}	Thoracic	Major surgery	Ketamine 400 μg ml^{-1}	Better in the ketamine group
116	24	Fentanyl 20 μg h^{-1} + 0.1% bupivacaine 10 mg h^{-1}	Thoracic	Major abdominal and thoracic	Epinephrine 2 μg ml^{-1}	Better in the epinephrine group
109	24	Morphine 100 μg h^{-1} + bupivacaine 5 mg h^{-1}	Thoracic	Lower abdominal	Clonidine 18.75 μg h^{-1}	Better pain relief but more hypotension
118	100	Fentanyl 10 μg h^{-1} + 0.125% bupivacaine 7.5 mg h^{-1} + PCEA fentanyl	Thoracic	Lower abdominal	Clonidine 2, 3 or 4 μg ml^{-1} 5 ml h^{-1}	Better pain relief with clonidine 20 μg h^{-1} but more hypotension

Although ketamine 400 μg ml^{-1}, used as an adjuvant to a low-dose epidural infusion of morphine, bupivacaine and adrenaline, enhanced dynamic pain relief,[30] concerns have been expressed about the lack of data on the potential neurotoxicity of ketamine,[173] Similarly, enthusiasm for the improved efficacy seen with the addition of clonidine 18–20 μg h^{-1} to thoracic epidural analgesia[118 109] is tempered by concerns about the increased incidence of hypotension and the increased level of surveillance needed. Although midazolam and verapamil have been used with bupivacaine, there are no data on their use as adjuvants to continuous epidural analgesia with LA–opioid combinations.

The addition or removal of adrenaline to a low-dose epidural mixture of bupivacaine and fentanyl has been investigated by Niemi and Breivik in a double-blind crossover study after major surgery.[116] The use of epinephrine was associated with minimal regression of the sensory block, markedly improved pain relief on coughing and reduced serum fentanyl concentrations. Despite concerns about the safety of adding vasoconstrictors to epidural mixtures, Breivik and colleagues have used this triple-component epidural mixture in over 6000 patients with apparent safety.[20]

Safety

There are a number of complications that can result from epidural analgesia, some of which are of major concern because of their potential to cause permanent neurological damage. Such adverse effects can be related to needle and catheter insertion, the presence of the catheter in the epidural space or the drugs infused, including drug errors. The introduction of Acute Pain Services has enabled early recognition of these diverse and, in some cases, extremely rare complications so that corrective action can be taken to prevent permanent harm.

Incidence of serious neurological complications due to epidural analgesia

Because of the rarity of permanent neurological damage resulting from epidural analgesia, it is difficult to estimate its incidence. In a combined series of more than 50 000 epidural anaesthetics, only three patients suffered permanent leg weakness (0.006%).[80] A retrospective study of 170 000 epidural anaesthetics in Finland over 10 yr and of the resulting claims for compensation revealed nine serious complications (0.005%): one case of paraparesis, one case of permanent cauda equina syndrome, one case of peroneal nerve paresis, one case of neurological deficit, two bacterial infections, two acute toxic reactions related to the anaesthetic solutions and one overdose of epidural opioid.[6] However, the incidence may be underestimated by such retrospective reviews. A prospective French study, involving 30 413 epidurals inserted over a 5-month period, revealed an incidence of severe complications of 0.04%: three cardiac arrests, four convulsions and six neurological injuries.[8] Although Giebler and colleagues found no permanent neurological deficit in a study of 4185 epidurals, the upper limit of his 95% confidence interval gives a predicted maximal risk for permanent neurological complications of 0.07%.[59] Dahlgren and Tornebrandt similarly reported an incidence of persistent neurological deficit of 0.03% after 9232 epidurals;[43] this is 10 times the risk given by Kane[80] and by Aromaa and colleagues.[6]

However, on many occasions the association between epidural anaesthesia/analgesia and serious neurological sequelae is only a temporal one and might be inappropriately suspected to be causal, as described in various case reports.[16 94 100 106 132]

Adverse events due to the insertion of needle and catheter

Dural puncture

Dural puncture occurs in 0.32–1.23% of epidural placements[59 138 155 172] and can result in the development of a postdural puncture headache. Rarely, subdural haematoma that can result in neurological deterioration has been described after dural puncture[58 75]; its incidence may be less with loss of resistance to saline than to air.[46 81 130] There is also a risk of pneumocephalus if air is used,[7 105] which can result in serious complications.[93 127 150] The use of saline may again help to reduce the incidence of this and other complications that have been associated with the use of air, notably spinal cord and nerve root compression and venous air embolism.[76 78 134 148] In addition, accidental pleural puncture during epidural catheter insertion has been described,[57 175] as has haemothorax.[74]

Direct trauma

Direct trauma to the spinal cord or peripheral nerves due to the needle or catheter is extremely rare, but has been reported. Epidural catheterization is most frequently performed in the awake patient to avoid this risk of neurological damage. This problem, which was highlighted in a recent case report,[22] is still being debated.[54] In support of epidural insertion in the anaesthetized patient, a recent study involving the placement of cerebrospinal fluid drainage needles and catheters in 530 anaesthetized patients undergoing neurosurgery reported no cases of nerve injury in the immediate postoperative period or within 1 yr of surgery.[63]

Transient neuropathy

Transient neuropathy with eventual full recovery occurs more commonly but is still relatively infrequent; a recent large prospective multicentre series involving 30 413 epidural anaesthetics reported five cases of radiculopathy (0.016%), over 50% recovering completely within 3 months.[8] This incidence is similar to previously published large studies on transient neuropathy: 4 out of 17 439 patients (0.023%)[155] and 0.013% from a retrospective study of 1 304 214 epidurals.[172] Other much smaller studies report an incidence of 0.24–0.56%.[59 138] A recent paediatric study found an incidence of up to 3%, but this involved small numbers of patients.[121] After certain operations, such as tibial fracture fixation, epidural analgesia has been implicated in a higher incidence of neurological complications.[73] However, a retrospective study demonstrated no significant association between the development of peroneal nerve palsy after total knee replacement and the use of postoperative epidural analgesia[66].

Adverse events due to the presence of an indwelling catheter in the epidural space

Spinal haematoma

Puncture of epidural vessels during catheter placement occurs during 3–12% of attempts.[143] However, the subsequent development of a spinal haematoma causing neurological damage is a rare complication. If not detected and treated early, it results in irreversible paraplegia. The incidence of clinically apparent epidural haematoma is unknown, as any study attempting to quantify it would have to involve an enormous number of patients. However, its occurrence does seem to be increasing, possibly as a result of increased use of regional anaesthesia in combination with altered coagulation [in particular low-molecular weight heparin (LMWH)] or of better reporting of the complication.

The risk of developing a spinal haematoma can be quantified only by either studying large numbers of routine or at-risk patients or collecting case reports of spinal haematoma after epidural blockade. The reported incidence varies greatly between studies. Vandermeulen and colleagues combined 18 studies involving 200 000 patients who received epidural analgesia and found no incidence of epidural haematoma.[161] In a review including 13 case series that involved >850 000 epidurals, there were only three cases of haematoma (0.0004%).[152] At the other extreme, three cases of epidural haematoma were reported after 9232 (0.03%) epidural insertions;[43] an even higher incidence, of two cases out of 1014 (0.2%) insertions, has also been reported.[144] On the basis of all available information, Tryba has given the best estimate for the risk of a spinal haematoma after epidural analgesia to be 1:150 000 at the upper 95% confidence interval.[158]

Examination of case reports of spinal haematoma has revealed potential risk factors, notably haemostatic abnormalities and/or anticoagulation, in particular the timing of catheter insertion and removal in relation to the administration of anticoagulants. In 61 cases of spinal haematoma associated with epidural/spinal anaesthesia, 42 (68%) of them had evidence of haemostatic abnormality: 30 had received heparin and 12 had evidence of coagulopathy or were treated with antiplatelet agents, thrombolytics or anticoagulants.[161] Forty-six of these had undergone epidural anaesthesia, 32 with the use of an epidural catheter. In nearly 50% of these 32 patients, the spinal haematoma occurred immediately after removal of the catheter, nine being removed when heparin concentrations were therapeutic. This demonstrates that development of a haematoma is not just related to insertion but also (of equal importance) to removal of the epidural catheter. Overall, 87% of epidural haematomas were related to some haemostatic abnormality or procedure difficulty. Literature concerning obstetric patients revealed 17 cases of haematoma after epidural catheter insertions, of which 14 (82%) had a bleeding diathesis.[135]

However, three studies involving over 5000 systemically anticoagulated patients and one study of 805 patients taking antiplatelet medication who received central neuraxial blockade described no cases of spinal haematoma.[10 70 117 123] Furthermore, four studies, involving intraoperative high-dose heparin during cardiac surgery in 776 adult patients and 234 paediatric patients who received central neuraxial blockade, failed to demonstrate any spinal haematoma formation, provided there were no other risk factors.[102 121 136 160]

The situation has changed dramatically with the introduction of LMWH as routine thromboembolic prophylaxis. A subsequent surge of epidural haematomas has ignited a very complex debate.[67] For detailed current recommendations, the reader is directed to a recent review by Horlocker and Wedel.[69] This review can be summarized as follows.

Oral anticoagulation. Catheter placement/removal should not be performed in fully anticoagulated patients. Epidural insertion is relatively safe, if low-dose warfarin (3–5 mg day^{-1}) is started after catheter insertion (192 patients).[71] An international normalized ratio (INR) of <1.4 at the time of catheter removal resulted in no case of spinal haematoma (459 patients).[170]

Intravenous and subcutaneous standard heparin. Systemic heparinization is safe for vascular surgery, if administered 60 min after catheter placement if coagulation is closely monitored and if the catheter is removed when circulating heparin concentrations are low.[123] Low-dose subcutaneous heparin in combination with epidural analgesia is safe—there were only three cases of spinal haematoma in the literature and none in a review of more than 5000 patients.[143]

LMWH. At least 40 cases of spinal haematoma have been reported in the USA with neuraxial anaesthesia under LMWH prophylaxis.[68] These were probably related to intraoperative or early postoperative administration, a twice-daily dosing schedule and concomitant antiplatelet therapy in the USA, as the European experience, with adherence to strict guidelines, is quite different. The worst incidence of spinal haematoma has been estimated at 1 in 3100 cases with continuous epidural analgesia under LMWH cover in the USA.[140] New recommendations follow the European guidelines, recommending 24-hourly dosing and a 12-h interval between LMWH injection and insertion or removal of the catheter.

Antiplatelet medications. It is relatively safe to insert an epidural whilst the patient is receiving antiplatelet medication; this is supported by several large studies involving obstetric and surgical patients.[5 72] No increased incidence of bloody tap was observed during epidural insertion in 1000 patients on antiplatelet medication, suggesting no difference in traumatic needle/catheter placement.[70]

Infection

Infection can be introduced into the epidural space from an exogenous source via contaminated equipment or drugs, or from an endogenous source, leading to bacteraemia, which seeds to the insertion site. Alternatively, the catheter can act as a wick through which infection tracks down from the entry site on the skin to the epidural space. Infection can result in meningitis (if the dura is breached) or epidural abscess formation, resulting in cord compression. It has been demonstrated that the spread of streptococci from the anaesthetist's buccal mucosa can cause epidural infections.[139] However, facemasks have not been shown to reduce the incidence of neuraxial infections.

Serious neuraxial infections after epidural anaesthesia have been reported as being rare. A review of 50 000 epidural anaesthetics did not show a single epidural or intrathecal infection[80] and, more recently, Dahlgren and Tornebrandt reported no cases of epidural abscess out of 9232 epidural insertions.[43] However, more recent, smaller studies cite the incidence as being closer to 1:10 000. A prospective Danish study, involving 17 372 epidural catheters, reported the incidence of epidural abscess to be 1:1930 (0.05%),[163] other studies giving similar figures of 2:13 000 and 2:2000.[84 133] The findings of the Danish study suggest that patients with epidural abscess had a longer mean catheterization time than the population mean, the majority of such patients were immunocompromised by one or more complicating diseases (malignancy, diabetes, multiple trauma, chronic obstructive respiratory disease) and perioperative anticoagulant therapy was involved in most cases.[163] There were no reports of abscess formation in patients with catheters *in situ* for 2 days or less. Predominance of immunocompromised patients has also been found in previous studies.[47 82] The risk of persistent neurological deficit from an epidural abscess is almost 50%, which may be explained by the long period from diagnosis of an epidural abscess to intervention;[163] this outcome has not improved since the period 1947–1974.[85]

Epidural analgesia in patients with known systemic or localized infection remains controversial. Many anaesthetists have considered sepsis to be a relative contraindication for epidural anaesthesia. It is generally recommended that epidural catheterization should not be performed in patients with untreated bacteraemia, unless there is an overwhelming reason to do so.[69] Jakobsen and colleagues, in a retrospective study of 69 patients with localized skin infections who underwent repeated epidural catheterization, reported no signs or symptoms of neuraxial infection.[77] However, another study reported three neuraxial infections related to epidural catheterization in patients with localized infections.[43] Small numbers in the studies make it difficult to provide recommendations.

Any patient with local or systemic infection is potentially at risk of developing neuraxial infection; extreme vigilance must be maintained in the monitoring and detection of epidural infection. There should be careful selection of patients currently responding to antibiotic treatment of their sepsis for which epidural analgesia is proposed. Also, the potential unproven risk of neuraxial infection after intraoperative transient bacteraemia during an obstetric or urological procedure should be considered. However, short-term catheterization in these patients is probably safe.[69]

Catheter migration

After initial placement of the epidural catheter in the epidural space, the tip of the catheter can move intrathecally. Similarly, i.v. migration can occur. Both must be considered before any bolus dose is administered via the epidural catheter by careful aspiration; a test dose of LA containing epinephrine can also provide evidence of i.v. migration by producing a transient tachycardia. These techniques, and the use of low-dose LA–opioid infusions, may help to prevent dramatic complications, such as total spinal anaesthesia with possible neurotoxicity[90] and seizures.[15 107 147] Unintentional subdural catheter placement or migration can also lead to a high block requiring intubation.[27]

The incidence of intrathecal migration has been reported as 0.15–0.18%[125 142] a similar figure of 0.18% has been reported for intravenous migration.[125]

Adverse events related to epidural drug administration

Drug errors

Most commonly, LAs, opioids and/or clonidine are infused into the epidural space to provide postoperative analgesia. All these drugs carry the potential for serious adverse effects. In addition, occasionally drug errors occur whereby the wrong drug is administered via the epidural catheter, sometimes resulting in tragic consequences. The incidence of such cases remains unclear as there are very few case reports—glucose,[167] antibiotics,[88] thiopentone,[26 55] potassium chloride[89 92 149] (resulting in paraplegia) and total parenteral nutrition[120] have all been inadvertently injected. The use of pharmacy-prepared or commercially prepared solutions, extreme care with labelling of epidural catheters and drugs, checking procedures and the use of dedicated pumps should help avoid these problems.

Respiratory depression

The side-effect of most concern with epidural opioids is respiratory depression. Because of the hydrophilic nature of some opioids, such as morphine, there is an increased tendency for the drug to remain in the CNS, particularly the cerebrospinal fluid, resulting in possible cephalad spread and delayed respiratory depression.

There is an abundance of literature devoted to neuraxial opioids and the incidence of respiratory depression. One Swedish review, encompassing 15 departments of anaesthesia, estimated an incidence of 0.25–0.4%, the major risk factors being age over 70 yr and additional administration of opioids by other routes.[64] A Canadian questionnaire, involving 56 teaching hospitals, cited an estimated incidence of 0.13%.[176] Although the choice of opioid is important, fentanyl or diamorphine being more lipophilic and less likely to cause delayed respiratory depression, the dose of drug given by continuous infusion is also important. To emphasize this point, there has been a case report describing three patients who developed severe respiratory depression during an epidural infusion containing bupivacaine and fentanyl 20–25 μg ml^{-1}.[164]

The actual, not estimated, incidence of respiratory depression has been reported in numerous studies involving data collection from an APS. The number of patients studied varies between 1014 and 1 304 214, with a reported incidence of 0.24–1.6%,[24 56 125 133 144 154 172] often associated with sedation.[91 144] The higher figures are more representative of the incidence using epidural morphine infusion. However, with the administration of epidural morphine <200 μg h^{-1} the risk of respiratory depression is probably no higher than with other epidural opioids.[21] Using a PCEA containing fentanyl and LA, the incidence is reported as 0.3%.[96]

The quoted incidence of respiratory depression when epidural analgesia is supervised by an APS is no higher than the incidence of respiratory depression seen with other forms of opioid analgesia.[19] Regular monitoring of respiratory rate and, more importantly, the level of consciousness appears to be adequate to detect respiratory depression, and is indicated for up to 12 h after a bolus injection of morphine and for the entire duration of a continuous infusion.

Table 6 Effective and safe management of ward-based epidural analgesia

Patient	Informed consent Careful selection based on a risk/benefit analysis and absence of contraindications
Regimen	Sterile technique Standard, pharmacy prepared or commercially produced low dose LA– opioid infusion Bupivacaine 8–12 mg h^{-1} plus fentanyl 2–4 µg ml^{-1} or morphine/diamorphine 50 µg ml^{-1} Standard infusion pump (different from i.v. PCA pumps) with PCEA facility Identifiable administration sets without injection ports Bacterial filter Transparent dressing
Staff	Training programme/protocols/acute pain handbook with particular attention to: Recognition and management of complications including hypotension, respiratory depression, inadequate analgesia and motor blockade Concurrent thromboprophylaxis and anticoagulant therapy Access to members of the acute pain team 24-h cover
Monitoring	Regular monitoring of dynamic pain scores, cardiorespiratory parameters, sedation scores, dermatomal level and motor blockade Daily inspection of the epidural site Twice daily review by the APT
Audit	Audit and feedback to anaesthetists, surgeons and nurses Critical incident reporting

Hypotension

Accompanying the sensory and motor block of epidural LAs are the sympatholytic effects due to blockade of the sympathetic chain; this results in hypotension. If the block height reaches the cardiac outflow between T1 and T5, there may be a marked hypotensive and bradycardic response, particularly in the presence of hypovolaemia. The degree of hypotension depends on the actual dose, lower concentrations of LA causing less effect on blood pressure. Unopposed parasympathetically mediated bronchoconstriction has also been proposed as the cause of a case of severe bronchospasm during epidural anaesthesia.[162]

Combining the results of three studies involving nearly 9000 patients, the incidence of hypotension during epidural infusion of LA is 0.7–3% depending on the concentration used (0.0625–0.25% bupivacaine) and the criteria for hypotension.[45 133 159] Use of a PCEA gave a 6.8% incidence of hypotension.[96]

The routine use of epidural clonidine up to 900 µg as boluses of 100 µg is likely to produce significant haemodynamic depression and sedation.[50 17 114] When infused at 20 µg h^{-1} with bupivacaine and fentanyl, it was shown to improve analgesia at rest and during coughing but, again, was associated with significant haemodynamic changes.[118]

CNS toxicity

The incidence of CNS toxicity, notably convulsions, as a result of high plasma concentrations of free LA, was reported to be 0.01–0.12% for bupivacaine when 16 870[23] and 40 010[155]epidural blocks were assessed There was a higher incidence of 0.3 per 1000 with lidocaine.[23] Cerebral irritation after doses as low as 30 mg h^{-1} has been described,[49] but this is still considerably higher than the 'optimal' dose of bupivacaine recommended by Curatolo and colleagues for LA–opioid combination.[40] A case of ropivacaine-induced seizure has been described after epidural anaesthesia.[1]

Motor blockade

Excessive lower limb motor blockade with controlled infusion of epidural LAs is uncommon, occurring in only in 3.0% of cases using low concentrations of bupivacaine.[144] If motor blockade does occur, it may result in the development of pressure areas on the heels[32 122 151] and deep venous thrombosis.[166] Persistent motor blockade of one or both lower limbs in a patient receiving a low dose combination LA–opioid thoracic epidural should always be treated with suspicion. Stopping the epidural infusion normally results in neurological improvement within 2 h. If this does not occur, consideration should be given to excluding a spinal haematoma or abscess. Ropivacaine may produce less motor blockade compared with an equianalgesic dose of bupivacaine,[174] especially if used in low concentrations (0.1%) with fentanyl (2 µg ml^{-1}).[98] Epidural blockade has been blamed in occasional case reports for masking the symptoms of compartment syndrome,[112 153 156] although there have also been cases which have been diagnosed successfully during epidural blockade.[12 111]

Organizational issues

Providing effective analgesia for patients undergoing major surgery is a daily challenge for most clinical anaesthetists. Continuous thoracic epidural analgesia with a low-dose LA–opioid combination has the potential to provide effective dynamic pain relief for many patients, even those undergoing major upper abdominal or thoracic procedures. This level of pain relief is central to early mobilization and rapid rehabilitation. However, in the hurly-burly of a busy surgical ward, it is not uncommon for epidurals to be ineffective in terms of providing dynamic pain relief. Rarely, and catastrophically, major damage to the patient may occur.

The major factors to be considered in the safe and effective management of ward-based epidural analgesia are shown in Table 6.

References

1 Abouleish EI, Elias M, Nelson C. Ropivacaine-induced seizure after extradural anaesthesia. *Br J Anaesth* 1998; **80**: 843–4

2 Aguilar JL, Cubells C, Rincon R, Preciado MJ, Valldeperas I, Vidal F. Pre-emptive analgesia following epidural 0.5% bupivacaine. In thoracotomy. *Reg Anesth* 1994; **19**: 72

3 Allaire PH, Messick JMJ, Oesterling JE, et *al.* A prospective randomized comparison of epidural infusion of fentanyl and intravenous administration of morphine by patient-controlled

analgesia after radical retropubic prostatectomy. *Mayo Clin Proc* 1992; **67**: 1031–1041

4 Andersen G, Rasmussen H, Rosenstock C, *et al.* Postoperative pain control by epidural analgesia after transabdominal surgery. Efficacy and problems encountered in daily routine. *Acta Anaesthesiol Scand* 2000; **44**: 296–301

5 Anonymous. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994; **343**: 619–29

6 Aromaa U, Lahdensuu M, Cozanitis DA. Severe complications associated with epidural and spinal anaesthesias in Finland 1987–1993. A study based on patient insurance claims. *Acta Anaesthesiol Scand* 1997; **41**: 445–52

7 Ash KM, Cannon JE, Biehl DR. Pneumocephalus following attempted epidural anaesthesia. *Can J Anaesth* 1991; **38**: 772–4

8 Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology* 1997; **87**: 479–86

9 Ballantyne JC, Carr DB, deFerranti S, *et al.* The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; **86**: 598–612

10 Baron HC, LaRaja RD, Rossi G, Atkinson D. Continuous epidural analgesia in the heparinized vascular surgical patient: a retrospective review of 912 patients. *J Vasc Surg* 1987; **6**: 144–6

11 Baxter AD, Laganiere S, Samson B, Stewart J, Hull K, Goernert L. A comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy analgesia. *Can J Anaesth* 1994; **41**: 184–91

12 Beerle BJ, Rose RJ. Lower extremity compartment syndrome from prolonged lithotomy position not masked by epidural bupivacaine and fentanyl. *Reg Anesth* 1993; **18**: 189–90

13 Benzon HT, Wong HY, Belavic JA, *et al.* A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. *Anesth Analg* 1993; **76**: 316–322

14 Berti M, Fanelli G, Casati A, *et al.* Patient supplemented epidural analgesia after major abdominal surgery with bupivacaine/fentanyl or ropivacaine/fentanyl. *Can J Anaesth* 2000; **47**: 27–32

15 Bhate H. Cerebral seizures during peridural anaesthesia (systemic reaction following bupivacaine 0.75%). *Reg Anaesth* 1983; **6**: 66–8

16 Bhuiyan MS, Mallick A, Parsloe M. Post-thoracotomy paraplegia coincident with epidural anaesthesia. *Anaesthesia* 1998; **53**: 583–586

17 Bonnet F, Boico O, Rostaing S, *et al.* Postoperative analgesia with extradural clonidine. *Br J Anaesth* 1989; **63**: 465–9

18 Boylan JF, Katz J, Kavanagh BP, et al. Epidural bupivacaine–morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. *Anesthesiology* 1998; **89**: 585–93

19 Breivik H. Safe perioperative spinal and epidural analgesia: Importance of drug combinations segmental site of injection, training and monitoring. *Acta Anaesthesiol Scand* 1995; **39**: 869–71

20 Breivik H, Hogstrom H, Niemi G, *et al.* Safe and effective postoperative pain relief: introduction and continuous quality-improvement of comprehensive postoperative pain management programmes. *Baillière's Clin Anaesthesiol* 1995; **9**: 423–60

21 Breivik H, Niemi G, Haugtomt H, Hogstrom H. Optimal epidural analgesia: importance of drug combinations and correct segmental site of injection. *Baillière's Clin Anaesthesiol* 1995; **9**: 493–512

22 Bromage PR, Benumof JL. Paraplegia following intracord injection during attempted epidural anesthesia under general anesthesia. *Reg Anesth Pain Med* 1998; **23**: 104–7

23 Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. *Anesth Analg* 1995; **81**: 321–8

24 Burstal R, Wegener F, Hayes C, Lantry G. Epidural analgesia: prospective audit of 1062 patients. *Anaesth Intens Care* 1998; **26**: 165–72

25 Callesen T, Schouenborg L, Nielsen D, Guldager H, Kehlet H. Combined epidural–spinal opioid-free anaesthesia and analgesia for hysterectomy. *Br J Anaesth* 1999; **82**: 881–5

26 Cay DL. Accidental epidural thiopentone. *Anaesth Intens Care* 1984; **12**: 61–3

27 Chauhan S, Gaur A, Tripathi M, Kaushik S. Unintentional combined epidural and subdural block. Case report. *Reg Anesth* 1995; **20**: 249–51

28 Chauvin M, Hongnat JM, Mourgeon E, Lebrault C, Bellenfant F, Alfonsi P. Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; **76**: 1251–8

29 Cheam EW, Morgan M. The superiority of epidural opioids for postoperative analgesia—fact or fallacy? *Anaesthesia* 1994; **49**: 1019–21

30 Chia Y-Y, Liu K, Liu Y-C, Chang H-C, Wong C-S. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. *Anesth Analg* 1998; **86**: 1245–9

31 Clinical Standards Advisory Group. Services for patients with pain. London: United Kingdom Stationery Office, 1999

32 Cohen S, Amar D, Pantuck CB, Pantuck EJ, Weissman AB. Adverse effects of epidural 0.03% bupivacaine during analgesia after cesarean section. *Anesth Analg* 1992; **75**: 753–6

33 Conacher ID, Paes ML, Jacobson L, Phillips PD, Heaviside DW. Epidural analgesia following thoracic surgery. A review of two years' experience. *Anaesthesia* 1983; **38**: 546–51

34 Cook TM, Eaton JM, Goodwin AP. Epidural analgesia following upper abdominal surgery: United Kingdom practice. *Acta Anaesthesiol Scand* 1997; **41**: 18–24

35 Cook TM, Riley RH. Analgesia following thoracotomy: a survey of Australian practice. *Anaesth Intens Care* 1997; **25**: 520–4

36 Cooper DW, Ryall DM, Desira WR. Extradural fentanyl for postoperative analgesia: predominant spinal or systemic action? *Br J Anaesth* 1995; **74**: 184–7

37 Cooper DW, Ryall DM, McHardy FE, Lindsay SL, Eldabe SS. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section. *Br J Anaesth* 1996; **76**: 611–5

38 Cooper DW, Saleh U, Taylor M, *et al.* Patient-controlled analgesia: epidural fentanyl and i.v. morphine compared after caesarean section. *Br J Anaesth* 1999; **82**: 366–370

39 Crews JC, Hord AH, Denson DD, Schatzman C. A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery. *Anesth Analg* 1999; **89**: 1504–9

40 Curatolo M, Schnider TW, Petersen-Felix S, *et al.* A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl, and clonidine for postoperative analgesia. *Anesthesiology* 2000; **92**: 325–37

41 Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Moiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *Br J Anaesth* 1992; **69**: 4–8

42 Dahl JB, Rosenberg J, Hansen BL, Hjortso NC, Kehlet H. Differential analgesic effects of low-dose epidural morphine and morphine–bupivacaine at rest and during mobilization after major abdominal surgery. *Anesth Analg* 1992; **74**: 362–5

43 Dahlgren N, Tornebrandt K. Neurological complications after anaesthesia. A follow-up of 18,000 spinal and epidural anaesthetics performed over three years. *Acta Anaesthesiol Scand* 1995; **39**: 872–80

44 De Leon-Casasola OA, Lema MJ. Postoperative epidural opioid analgesia: what are the choices?. *Anesth Analg* 1996; **83**: 867–75

45 De Leon-Casasola OA, Parker B, Lema MJ, Harrison P, Massey J. Postoperative epidural bupivacaine–morphine therapy. Experience with 4,227 surgical cancer patients. *Anesthesiology* 1994; **81**: 368–75

46 Diemunsch P, Balabaud VP, Petiau C, *et al.* Bilateral subdural hematoma following epidural anesthesia. *Can J Anaesth* 1998; **45**: 328–31

47 Du Pen SL, Peterson DG, Williams A, Bogosian AJ. Infection during chronic epidural catheterization: diagnosis and treatment. *Anesthesiology* 1990; **73**: 905–9

48 Duncan LA, Fried MJ, Lee A, Wildsmith JA. Comparison of continuous and intermittent administration of extradural bupivacaine for analgesia after lower abdominal surgery. *Br J Anaesth* 1998; **80**: 7–10

49 Dunne NM, Kox WJ. Neurological complications following the use of continuous extradural analgesia with bupivacaine. *Br J Anaesth* 1991; **66**: 617–9

50 Eisenach JC, Lysak SZ, Viscomi CM. Epidural clonidine analgesia following surgery: Phase I. *Anesthesiology* 1989; **71**: 640–6

51 Espinet A, Henderson DJ, Faccenda KA, Morrison LMM. Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy. *Br J Anaesth* 1996; **76**: 209–13

52 Etches RC, Gammer T-L, Cornish R. Patient-controlled epidural analgesia after thoracotomy: A comparison of meperidine with and without bupivacaine. *Anesth Analg* 1996; **83**: 81–6

53 Etches RC, Writer WD, Ansley D, *et al.* Continuous epidural ropivacaine 0.2% for analgesia after lower abdominal surgery. *Anesth Analg* 1997; **84**: 784–90

54 Fischer HB. Regional anaesthesia—before or after general anaesthesia? *Anaesthesia* 1998; **53**: 727–9

55 Forestner JE, Raj PP. Inadvertent epidural injection of thiopental: a case report. *Anesth Analg* 1975; **54**: 406–7

56 Fuller JG, McMorland GH, Douglas MJ, Palmer L. Epidural morphine for analgesia after caesarean section: a report of 4880 patients. *Can J Anaesth* 1990; **37**: 636–40

57 Furuya A, Matsukawa T, Ozaki M, Kumazawa T. Interpleural misplacement of an epidural catheter. *J Clin Anesth* 1998; **10**: 425–6

58 Garcia-Sanchez MJ, Prieto-Cuellar M, Sanchez-Carrion JM, Galdo-Abadin JR, Martin-Linares JM, Horcajadas-Almansa A. Chronic subdural hematoma secondary to an accidental dural puncture during lumbar epidural anesthesia. *Rev Esp Anestesiol Reanim* 1996; **43**: 327–9

59 Giebler RM, Scherer RU, Peters J. Incidence of neurologic complications related to thoracic epidural catheterization. *Anesthesiology* 1997; **86**: 55–63

60 Gopinathan C, Sockalingham I, Fung MA, Peat S, Hanna MH. A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17**: 189–96

61 Gottschalk A, Smith DS, Jobes DR, *et al.* Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. *J Am Med Assoc* 1998; **279**: 1076–82

62 Gourlay GK, Lowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration analgesia response relationship in the treatment of postoperative pain. *Anesth Analg* 1988; **67**: 327–8

63 Grady RE, Horlocker TT, Brown RD, Maxson PM, Schroeder DR. Neurologic complications after placement of cerebrospinal fluid drainage catheters and needles in anesthetized patients: implications for regional anesthesia. Mayo Perioperative Outcomes Group. *Anesth Analg* 1999; **88**: 388–92

64 Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; **54**: 479–86

65 Hjortso NC, Lund C, Mogensen T, Bigler D, Kehlet H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesth Analg* 1986; **65**: 1033–6

66 Horlocker TT, Cabanela ME, Wedel DJ. Does postoperative epidural analgesia increase the risk of peroneal nerve palsy after total knee arthroplasty? *Anesth Analg* 1994; **79**: 495–500

67 Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. *Reg Anesth Pain Med* 1998a; **23**: 164–77

68 Horlocker TT, Wedel DJ. Spinal and epidural blockade and perioperative low molecular weight heparin: smooth sailing on the Titanic. *Anesth Analg* 1998b; **86**: 1153–6

69 Horlocker TT, Wedel DJ. Neurologic complications of spinal and epidural anesthesia. *Reg Anesth Pain Med* 2000; **25**: 83–98

70 Horlocker TT, Wedel DJ, Offord KP. Does preoperative antiplatelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? *Anesth Analg* 1990; **70**: 631–4

71 Horlocker TT, Wedel DJ, Schlichting JL. Postoperative epidural analgesia and oral anticoagulant therapy. *Anesth Analg* 1994; **79**: 89–93

72 Horlocker TT, Wedel DJ, Schroeder DR, *et al.* Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995; **80**: 303–9

73 Iaquinto JM, Pienkowski D, Thornsberry R, Grant S, Stevens DB. Increased neurologic complications associated with postoperative epidural analgesia after tibial fracture fixation. *Am J Orthop* 1997; **26**: 604–8

74 Iida Y, Kashimoto S, Matsukawa T, Kumazawa T. A hemothorax after thoracic epidural anesthesia. *J Clin Anesth* 1994; **6**: 505–7

75 Jack TM. Post-partum intracranial subdural haematoma. A possible complication of epidural analgesia. *Anaesthesia* 1979; **34**: 176–80

76 Jackson KE, Rauck RL. Suspected venous air embolism during epidural anesthesia. *Anesthesiology* 1991; **74**: 190–1

77 Jakobsen KB, Christensen MK, Carlsson PS. Extradural anaesthesia for repeated surgical treatment in the presence of infection. *Br J Anaesth* 1995; **75**: 536–40

78 Jennings AL, Rothwell MP, Naysmith A. Epidural complications and a case of malignant meningitis. *Palliative Med* 1997; **11**: 483–6

79 Kampe S, Weigand C, Kaufmann J, Klimek M, Konig DP, Lynch J. Postoperative analgesia with no motor block by continuous epidural infusion of ropivacaine 0.1% and sufentanil after total hip replacement. *Anesth Analg* 1999; **89**: 395–8

80 Kane RE. Neurologic deficits following epidural or spinal anesthesia. *Anesth Analg* 1981; **60**: 150–61

81 Katz Y, Markovits R, Rosenberg B. Pneumoencephalus after inadvertent intrathecal air injection during epidural block. *Anesthesiology* 1990; **73**: 1277–9

82 Kee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for caesarean section. *Br J Anaesth* 1992; **69**: 647–52

83 Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87**: 62–72.

84 Kindler C, Seeberger M, Siegemund M, Schneider M. Extradural abscess complicating lumbar extradural anaesthesia and analgesia in an obstetric patient. *Acta-Anaesthesiol Scand* 1996; **40**: 858–61

85 Kindler CH, Seeberger MD, Staender SE. Epidural abscess complicating epidural anesthesia and analgesia. An analysis of the literature. *Acta Anaesthesiol Scand* 1998; **42**: 614–20

86 Komatsu H, Matsumoto S, Mitsuhata H, Abe K, Toriyabe S. Comparison of patient-controlled epidural analgesia with and without background infusion after gastrectomy. *Anesth Analg* 1998; **87**: 907–10

87 Kopacz DJ, Sharrock NE, Allen HW. A comparison of levobupivacaine 0.125%, fentanyl 4 µg/ml, or their combination for patient-controlled epidural analgesia after major orthopedic surgery. *Anesth Analg* 1999; **89**: 1497–503

88 Kopacz DJ, Slover RB. Accidental epidural cephazolin injection: safeguards for patient-controlled analgesia. *Anesthesiology* 1990; **72**: 944–7

89 Kulka PJ, Stratesteffen I, Grunewald R, Wiebalck A. Inadvertent potassium chloride infusion in an epidural catheter. *Anaesthesist* 1999; **48**: 896–9

90 Lee DS, Bui T, Ferrarese J, Richardson PK. Cauda equina syndrome after incidental total spinal anesthesia with 2% lidocaine. *J Clin Anesth* 1998; **10**: 66–9

91 Leith S, Wheatley RG, Jackson IJ, Madej TH, Hunter D. Extradural infusion analgesia for postoperative pain relief. *Br J Anaesth* 1994; **73**: 552–8

92 Lin D, Becker K, Shapiro HM. Neurologic changes following epidural injection of potassium chloride and diazepam: a case report with laboratory correlations. *Anesthesiology* 1986; **65**: 210–2

93 Lin HY, Wu HS, Peng TH, *et al.* Pneumocephalus and respiratory depression after accidental dural puncture during epidural analgesia—a case report. *Acta Anaesthesiol Sin* 1997; **35**: 119–23

94 Linz SM, Charbonnet C, Mikhail MS, *et al.* Spinal artery syndrome masked by postoperative epidural analgesia. *Can J Anaesth* 1997; **44**: 1178–81

95 Liu S, Angel JM, Owens BD, Carpenter RL, Isabel L. Effects of epidural bupivacaine after thoracotomy. *Reg Anesth* 1995; **20**: 303–10

96 Liu SS, Allen HW, Olsson GL. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards: prospective experience with 1,030 surgical patients. *Anesthesiology* 1998; **88**: 688–95

97 Liu SS, Carpenter RL, Mackey DC, *et al.* Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995; **83**: 757–765

98 Liu SS, Moore JM, Luo AM, Trautman WJ, Carpenter RL. Comparison of three solutions of ropivacaine/fentanyl for postoperative patient-controlled epidural analgesia. *Anesthesiology* 1999; **90**: 727–33

99 Loper KA, Ready LB, Downey M, *et al.* Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. *Anesth Analg* 1990; **70**: 72–5

100 Lovstad RZ, Steen PA, Forsman M. Paraplegia after thoracotomy—not caused by the epidural catheter. *Acta Anaesthesiol Scand* 1999; **43**: 230–2

101 Lowson SM, Alexander JI, Black AMS, Bambridge AD. Epidural diamorphine infusions with and without 0.167% bupivacaine for postoperative analgesia. *Eur J Anaesthesiol* 1994; **11**: 345–52

102 Maeda M, Kosaka Y, Kushizaki H, Yamamori Y, Hashimoto K, Saito Y. Safety of continuous epidural anesthesia during heart surgery–change of coagulation-fibrinolysis under heparinization. *Masui Jpn J Anesthiol* 1999; **48**: 723–30

103 Mahon SV, Berry PD, Jackson M, Russell GN, Pennefather SH. Thoracic epidural infusions for post-thoracotomy pain: a comparison of fentanyl-bupivacaine mixtures vs. fentanyl alone. *Anaesthesia* 1999; **54**: 641–6

104 Mann C, Pouzeratte Y, Boccara G, *et al.* Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000; **92**: 433–41

105 Mateo E, Lopez-Alarcon MD, Moliner S, *et al.* Epidural and subarachnoidal pneumocephalus after epidural technique. *Eur J Anaesthesiol* 1999; **16**: 413–7

106 Matsuura JA, Makhoul RG, Posner MP, Smith J, Litwack RS. Intradural herniation of a thoracic disc causing paraplegia coincident with epidural anesthesia. *Anesth Analg* 1997; **84**: 922–3

107 Miguel R, Barlow I, Morrell M, Scharf J, Sanusi D, Fu E. A prospective, randomized, double-blind comparison of epidural and intravenous sufentanil infusions. *Anesthesiology* 1994; **81**: 346–52

108 Mitchell RWD, Scott DB, Holmquist E, Lamont M. Continuous extradural infusion of 0.125% bupivacaine for pain relief after lower abdominal surgery. *Br J Anaesth* 1988; **60**: 851–3

109 Mogensen T, Eliasen K, Ejlersen E, Vegger P, Nielsen IK, Kehlet H. Epidural clonidine enhances postoperative analgesia from a combined low-dose epidural bupivacaine and morphine regimen. *Anesth Analg* 1992; **75**: 607–10

110 Mogensen T, Hjortso N-C, Bigler D, Lund C, Kehlet H. Unpredictability of regression of analgesia during the continuous postoperative extradural infusion of bupivacaine. *Br J Anaesth* 1988; **60**: 515–9

111 Montgomery CJ, Ready LB. Epidural opioid analgesia does not obscure diagnosis of compartment syndrome resulting from prolonged lithotomy position. *Anesthesiology* 1991; **75**: 541–3

112 Morrow BC, Mawhinney IN, Elliott JR. Tibial compartment syndrome complicating closed femoral nailing: diagnosis delayed by an epidural analgesic technique—case report. *J Trauma-Inj Infect Crit Care* 1994; **37**: 867–8

113 Motamed C, Spencer A, Farhat F, Bourgain JL, Lasser P, Jayr C. Postoperative hypoxaemia: Continuous extradural infusion of bupivacaine and morphine vs patient-controlled analgesia with intravenous morphine. *Br J Anaesth* 1998; **80**: 742–747

114 Motsch J, Graber E, Ludwig K. Addition of clonidine enhances postoperative analgesia from epidural morphine: a double-blind study. *Anesthesiology* 1990; **73**: 1067–1073

115 Mourisse J, Hasenbos MA, Gielen MJ, Moll JE, Cromheecke GJ. Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain. *Acta Anaesthesiol Scand* 1992; **36**: 70–74

116 Niemi G, Breivik H. Adrenaline markedly improves thoracic epidural analgesia produced by a low-dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomised, double-blind, cross-over study with and without adrenaline. *Acta Anaesthesiol Scand* 1998; **42**: 897–909

117 Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia* 1983; **38**: 254–9

118 Paech MJ, Pavy TJ, Orlikowski CE, Lim W, Evans SF. Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in combination with bupivacaine and fentanyl. *Anesth Analg* 1997; **84**: 1323–8

119 Paech MJ, Westmore MD. Postoperative epidural fentanyl infusion—is the addition of 0.1% bupivacaine of benefit? *Anaesth Intens Care* 1994; **22**: 9–14

120 Patel PC, Sharif AM, Farnando PU. Accidental infusion of total parenteral nutrition solution through an epidural catheter. *Anaesthesia* 1984; **39**: 383–4

121 Peterson KL, DeCampli WM, Pike NA, Robbins RC, Reitz BA. A report of two hundred twenty cases of regional anesthesia in pediatric cardiac surgery. *Anesth Analg* 2000; **90**: 1014–9

122 Punt CD, van Neer PA, de Lange S. Pressure sores as a possible complication of epidural analgesia. *Anesth Analg* 1991; **73**: 657–9

123 Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology* 1981; **55**: 618–20

124 Ready LB. Acute pain: lessons learned from 25,000 patients. *Reg Anesth Pain Med* 1999; **24**: 499–505

125 Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. *Anesthesiology* 1991; **75**: 452–6

126 Richards JT, Read JR, Chambers WA. Epidural anaesthesia as a method of pre-emptive analgesia for abdominal hysterectomy. *Anaesthesia* 1998; **53**: 296–8

127 Rodrigo P, Garcia JM, Ailagas J. General convulsive crisis related to pneumocephalus after inadvertent dural puncture in an obstetric patient. *Rev Esp Anestesiol Reanim* 1997; **44**: 247–9

128 Rolf N, Van Aken H. Physiology and pathophysiology of thoracic sympathetic blockade. Thoracic Epidural Anaesthesia. *Baillière's Clin Anaesthesiol* 1999; 13: 1–7

129 Romer HC, Russell GN. A survey of the practice of thoracic epidural analgesia in the United Kingdom. *Anaesthesia* 1998; **53**: 1016–22

130 Rosenow F, Huber M, Scheidt W, Heiss WD. Neurological cause of late postpartum seizures. *Arch Gynecol Obstet* 1991; **248**: 151–5

131 Ross RA, Clarke JE, Armitage EN. Postoperative pain prevention by continuous epidural infusion. A study of the clinical effects and the plasma concentrations obtained. *Anaesthesia* 1980; **35**: 663–8

132 Rutter SV, Jeevananthan V, Souter R, Cowen MJ. 'Shared spinal cord' scenario: paraplegia following abdominal aortic surgery under combined general and epidural anaesthesia. *Eur J Anaesthesiol* 1999; **16**: 646–9

133 Rygnestad T, Borchgrevink PC, Eide E. Postoperative epidural infusion of morphine and bupivacaine is safe on surgical wards. Organisation of the treatment, effects and side-effects in 2000 consecutive patients. *Acta Anaesthesiol Scand* 1997; **41**: 868–76

134 Saberski LR, Kondamuri S, Osinubi OY. Identification of the epidural space: is loss of resistance to air a safe technique? A review of the complications related to the use of air. *Reg Anesth* 1997; **22**: 3–15

135 Sage DJ. Epidurals, spinals and bleeding disorders in pregnancy: a review. *Anaesth Intens Care* 1990; **18**: 319–26

136 Sanchez R, Nygard E. Epidural anesthesia in cardiac surgery: is there an increased risk? *J Cardiothorac Vasc Anesth* 1998; **12**: 170–3

137 Sandler AN, Stringer D, Panos L, *et al.* A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief: analgesic, pharmacokinetic, and respiratory effects. *Anesthesiology* 1992; **77**: 626–34

138 Scherer R, Schmutzler M, Giebler R, Erhard J, Stocker L, Kox WJ. Complications related to thoracic epidural analgesia: a prospective study in 1071 surgical patients. *Acta Anaesthesiol Scand* 1993; **37**: 370–4

139 Schneeberger PM, Janssen M, Voss A. Alpha-hemolytic streptococci: a major pathogen of iatrogenic meningitis following lumbar puncture. Case reports and a review of the literature. *Infection* 1996; **24**: 29–33

140 Schroeder DR. Statistics: detecting a rare adverse drug reaction using spontaneous reports. *Reg Anesth Pain Med* 1998; **23**: 183–9

141 Schug SA, Scott DA, Payne J, Mooney PH, Hagglof B. Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* 1996; **76**: 487–91

142 Schug SA, Torrie JJ. Safety assessment of postoperative pain management by an acute pain service. *Pain* 1993; **55**: 387–91

143 Schwander D, Bachmann F. Heparin and spinal or epidural anesthesia: decision analysis. *Ann Fr Anesth Reanim* 1991; **10**: 284–96

144 Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. *Anesthesiology* 1995; **83**: 727–37

145 Scott DA, Blake D, Buckland M, *et al.* A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 μg/mL fentanyl for seventy-two h of postoperative analgesia after major abdominal surgery. *Anesth Analg* 1999; **88**: 857–64

146 Scott NB, Mogensen T, Bigler D, Lund C, Kehlet H. Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response. *Br J Anaesth* 1989; **62**: 253–7

147 Seeling W, Heinrich H. Unexpected intravenous penetration of an epidural catheter. *Reg Anaesth* 1984; **7**: 137–9

148 Sethna NF, Berde CB. Venous air embolism during identification of the epidural space in children. *Anesth Analg* 1993; **76**: 925–7

149 Shanker KB, Palkar NV, Nishkala R. Paraplegia following epidural potassium chloride. *Anaesthesia* 1985; **40**: 45–7

150 Sherer DM, Onyeije CI, Yun E. Pneumocephalus following inadvertent intrathecal puncture during epidural anesthesia: a case report and review of the literature. *J Maternal-Fetal Med* 1999; **8**: 138–40

151 Smet IG, Vercauteren MP, De Jongh RF, Vundelinckx GJ, Heylen RJ. Pressure sores as a complication of patient-controlled epidural analgesia after cesarean delivery. Case report. *Reg Anesth* 1996; **21**: 338–41

152 Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth* 1996; **43**: 129–41

153 Strecker WB, Wood MB, Bieber EJ. Compartment syndrome masked by epidural anesthesia for postoperative pain. Report of a case. *J Bone Joint Surg Am Vol* 1986; **68**: 1447–8

154 Stuart-Taylor ME, Billingham IS, Barrett RF, Church JJ. Extradural diamorphine for postoperative analgesia: audit of a nurse-administered service to 800 patients in a district general hospital. *Br J Anaesth* 1992; **68**: 429–32

155 Tanaka K, Watanabe R, Harada T, Dan K. Extensive application of epidural anesthesia and analgesia in a university hospital: incidence of complications related to technique. *Reg Anesth* 1993; **18**: 34–8

156 Tang WM, Chiu KY. Silent compartment syndrome complicating total knee arthroplasty: continuous epidural anesthesia masked the pain. *J Arthroplasty* 2000; **15**: 241–3

157 Torda TA, Hann P, Mills G, De Leon G, Penman D. Comparison of extradural fentanyl, bupivacaine and two fentanyl–bupivacaine mixtures for pain relief after abdominal surgery. *Br J Anaesth* 1995; **74**: 35–40

158 Tryba M. Epidural regional anesthesia and low molecular heparin: Pro. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1993; **28**: 179–81

159 Tsui SL, Irwin MG, Wong CM, *et al.* An audit of the safety of an acute pain service. *Anaesthesia* 1997; **52**: 1042–7

160 Turfrey DJ, Ray DA, Sutcliffe NP, Ramayya P, Kenny GN, Scott NB. Thoracic epidural anaesthesia for coronary artery bypass graft surgery. Effects on postoperative complications. *Anaesthesia* 1997; **52**: 1090–5

161 Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; **79**: 1165–77

162 Wang CY, Ong GS. Severe bronchospasm during epidural anaesthesia. *Anaesthesia* 1993; **48**: 514–5

163 Wang LP, Hauerberg J, Schmidt JF. Incidence of spinal epidural abscess after epidural analgesia: a national 1-year survey. *Anesthesiology* 1999; **91**: 1928–36

164 Weightman WM. Respiratory arrest during epidural infusion of bupivacaine and fentanyl. *Anaesth Intens Care* 1991; **19**: 282–4

165 Welchew EA. The optimum concentration for epidural fentanyl. A randomised, double-blind comparison with and without 1: 200 000 adrenaline. *Anaesthesia* 1983; **38**: 1037–41

166 Wheatley RG, Madej TH, Jackson IJB, Hunter D. The first year's experience of an acute pain service. *Br J Anaesth* 1991; **67**: 353–9

167 Whiteley MH, Laurito CE. Neurologic symptoms after accidental administration of epidural glucose. *Anesth Analg* 1997; **84**: 216–7

168 Wiebalck A, Brodner G, Van Aken H. The effects of adding sufentanil to bupivacaine for postoperative patient-controlled epidural analgesia. *Anesth Analg* 1997; **85**: 124–9

169 Woolf CJ, Chong M-S. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; **77**: 362–79

170 Wu CL, Perkins FM. Oral anticoagulant prophylaxis and epidural catheter removal. *Reg Anesth* 1996; **21**: 517–24

171 Wu CT, Yeh CC, Yu JC, *et al.* Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. *Acta Anaesthesiol Scand* 2000; **44**: 63–8

172 Xie R, Liu YP. Survey of the use of epidural analgesia in China. *Chin Med J* 1991; **104**: 510–5

173 Yaksh TL. Epidural ketamine: a useful, mechanistically novel adjuvant for epidural morphine? *Reg Anesth* 1996; **21**: 508–13

174 Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: a double-blind study. *Reg Anesth* 1996; **21**: 14–25

175 Zaugg M, Stoehr S, Weder W, Zollinger A. Accidental pleural puncture by a thoracic epidural catheter. *Anaesthesia* 1998; **53**: 69–71

176 Zimmermann DL, Stewart J. Postoperative pain management and acute pain service activity in Canada. *Can J Anaesth* 1993; **40**: 568–75

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Effect of postoperative analgesia on surgical outcome

H. Kehlet* and K. Holte

Department of Surgical Gastroenterology, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark
**Corresponding author*

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Despite improvements in perioperative care, major surgical operations are still followed by sequelae such as pain, organ dysfunction and prolonged convalescence. It has been assumed that sufficient pain relief will improve the surgical outcome with reduced morbidity, need for hospitalization and convalescence, and there is a common consensus that optimal (dynamic) pain relief is a prerequisite for early postoperative recovery. However, in recent years it has been realized that several other factors in perioperative management are important in the control of postoperative recovery and rehabilitation, and that these factors must be considered and revised in order to achieve the advantageous effects of pain relief on outcome.[39] Among the most commonly used pain-relieving techniques [patient-controlled analgesia (PCA) with opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and epidural analgesic techniques], there is evidence that the epidural local anaesthetic or local anaesthetic–opioid techniques are the most effective on providing dynamic pain relief after major surgical procedures.[43 79] This paper reviews data from randomized controlled trials on the effects of these analgesic techniques on postoperative morbidity and hospital stay (with emphasises on epidural analgesia) in order to derive useful conclusions on the relationship between optimal pain relief and postoperative outcome.[39] The effect of peripheral nerve blocks on postoperative morbidity will not be dealt with in this review.

Effect of postoperative pain relief on surgical stress responses

It has been hypothesized that a reduction in the surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome.[39] As afferent neural stimuli and activation of the autonomic nervous system and other reflexes by pain may serve as a major release mechanism of the endocrine metabolic responses and thus contribute to various organ dysfunctions, pain relief may be a powerful technique to modify surgical stress responses. However, there is a pronounced differential effect of the various postoperative pain-relieving techniques on surgical stress responses (Table 1). Only regional anaesthetic techniques, and preferably continuous techniques with local anaesthetic, may lead to a substantial reduction in the surgical stress response.[40] Thus, several studies investigating lower extremity surgery have shown continuous lumbar epidural local anaesthetic techniques to be most effective, probably because of a more effective afferent blockade. In abdominal procedures, there is a somewhat smaller efficacy of thoracic epidural local anaesthetic techniques in modulating endocrine-metabolic responses, probably due to insufficient afferent blockade as well as the presence of other release mechanisms in eliciting the surgical stress response. The duration of epidural local anaesthetic analgesia is important; it should be at least 24 h and preferably 48 h.[40]

Epidural opioid techniques are less effective on the stress response, and are comparable with systemic opioid techniques and the use of NSAIDs. High-dose opioid anaesthesia suppresses intra- but not postoperative responses.[40] There are insufficient data on the use of multimodal analgesic techniques with combinations of different analgesics. It will be emphasized here that analgesic management predominantly will reduce endocrine metabolic responses[40] and that other techniques, such as minimally invasive surgery and the use of high-dose glucocorticoids, are needed to reduce the inflammatory responses.[39]

Effect of patient-controlled analgesia on postoperative outcome

PCA is widely used for many surgical procedures and is of clear benefit as patient satisfaction is improved,[5] and

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Table 1 Effects of analgesic techniques on postoperative surgical stress responses (adapted from reference 40). =no effect; ↓=small effect; ↓↓=moderate effect; ↓↓↓=major effect

Type of analgesia	**Endocrine–metabolic responses**	**Inflammatory responses**
Systemic opioid (PCA or intermittent)	↓	
NSAID	↓	↓
Epidural opioid	↓	
Lumbar epidural local anaesthetics (lower extremity surgery)	↓↓↓	
Thoracic epidural local anaesthetics (abdominal surgery)	↓↓	

nursing time somewhat decreased.[10, 14] However, PCA will not provide optimal dynamic pain relief after major procedures[38] and a meta-analysis[5] and more recent randomized studies[10, 14, 16, 20, 25, 44, 59] have demonstrated clearly that postoperative morbidity (pulmonary-, cardiac- and thromboembolic complications and hospital stay) is not improved by PCA compared with intermittent opioid therapy. These rather disappointing findings are consistent with the lack of effect of PCA on surgical stress responses and organ dysfunction.[39, 40]

Non-steroidal anti-inflammatory agents

NSAIDs are widely used for perioperative pain control but have little effect on surgical stress responses and organ dysfunction.[39, 40] On the other hand, it is well established that NSAIDs provide moderate postoperative analgesia and thereby an opioid-sparing effect of 20–30%.[61] This may be of clinical importance as NSAIDs may reduce the incidence of opioid-related side-effects (respiratory depression, sedation, nausea and vomiting, ileus, urinary bladder dysfunction and possibly sleep disturbances). Many randomized, controlled studies of perioperative NSAID treatment have been performed, but they have often included a variety of surgical procedures and a relatively small number of patients, thereby preventing firm conclusions about the clinical implications of opioid-sparing therapy.[42, 61] A meta-analysis of these studies has not been performed, but in narrative reviews a significant reduction in opioid-related side-effects has been obtained in only 20–30% of the reported randomized studies with opioid sparing and NSAIDs.[42, 61] Future large-scale randomized studies are required in well-defined surgical procedures to quantify the clinically relevant effects of NSAID-induced opioid-sparing on postoperative outcome.

Epidural analgesic techniques

Because continuous epidural local anaesthetic techniques are the most effective in reducing surgical stress responses, autonomic reflex responses and subsequently organ dysfunctions, a substantial reduction in postoperative morbidity may be expected.[23, 40, 48] Furthermore, they are the most effective method of providing dynamic pain relief after major procedures.[38, 79]

However, the literature has been confounded by many misunderstandings in different narrative reviews and meta-analyses. Studies with different types of epidural analgesic techniques have been combined. This is not rational as opioid-based regimens have less or no effect on stress responses and organ dysfunction compared with local anaesthetic-based regimens.[40] Furthermore, a variety of surgical procedures have been included in these studies, which may limit interpretation of the findings as the effects on stress responses and organ dysfunction are less pronounced in major abdominal and thoracic procedures compared with lower body procedures.[40] Thus, the level of epidural blockade is of major importance, in particular the distinction between thoracic and lumbar blockade. Also, definitions of adverse outcomes have varied. Finally, outcome effects have to be distinguished for single-dose and continuous regional anaesthetic/analgesic techniques.

The outcome of intra- and early postoperative analgesia by single-dose regional anaesthetic techniques (epidural and spinal anaesthesia) has been discussed for decades. A recent meta-analysis of all randomized studies,[65] including 141 trials in a total of 9559 patients, concluded that central neuraxial blockade reduces the risk of deep venous thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, respiratory depression by 59% and myocardial infarction by 30%. Mortality was reduced by 30%. These positive findings were obtained predominantly after major orthopaedic procedures, whereas no significant effects were found in other procedures (urological, abdominal and thoracic). Because most studies involved single-dose regimens, the data did not allow any conclusions about the effect of continuous regional anaesthetic techniques on postoperative morbidity.[65] In this article, an updated review of the effect on continuous epidural techniques (including local anaesthetics, local anaesthetic–opioid combinations and opioids) compared with opioid techniques as assessed in randomized, controlled studies is presented with respect to postoperative complications/morbidity. The data focus primarily on pulmonary and cardiac complications, postoperative paralytic ileus, thromboembolic and cerebral complications, and hospital stay.

Pulmonary complications

The impairment of pulmonary function observed after all major procedures may contribute to the development of hypoxaemia, atelectases and pneumonia. The superior pain relief provided by thoracic epidural local anaesthetic techniques may therefore be expected to reduce pulmonary morbidity by modifying these responses as well as by reducing opioid requirements. In a meta-analysis from 1998[6] on the effect of epidural versus systemic analgesia in

Table 2 Effects of epidural analgesia on pulmonary complications. We define pulmonary complications as clinically diagnosed pneumonia and/or respiratory failure occurring after recovery from anaesthesia. Respiratory failure is defined as reintubation, not prolonged mechanical ventilation. Respiratory depression, reversible by naloxone, is not considered as respiratory failure but as a side-effect of the analgesia administered. Studies which only evaluated atelectasis, non-specified clinical complications or radiologically diagnosed lung changes are marked [a]. In studies marked [b], a well-defined clinical assessment scale to evaluate pulmonary adverse outcome was developed. However, these scales are not widely accepted clinically and may hinder exact comparison between studies. We counted the number of patients with pneumonia and/or respiratory failure. As several studies count the number of complications and not the number of patients with complications, it cannot be excluded that patients with pneumonia also developed respiratory failure, thus being counted twice. Congruent epidural catheter placement is defined as thoracic placement (epidural catheter placed entirely in the thoracic column) for abdominal and thoracic procedures, and lumbar placement for lower extremity surgery. Because of the established central effects of epidural opioid administration, congruent catheter placement is only relevant when administering epidural local anaesthetics. As the effects of epidural saline are unclear, we have chosen not to include study groups receiving epidural saline in our analysis. Studies in which several types of epidural analgesia were evaluated (against the same control group) are marked [c]. In one study [d], surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study [e], respiratory failure consisted of a mixture of prolonged ventilation and reintubation, and the incidence of pneumonia was counted together with other major infections, and is therefore not available for analysis. Lower extremity procedures includes vascular surgery (Table 2A). Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery (Table 2B and C). Major thoracic surgery includes all non-cardiac intrathoracic procedures (Table 2C). LA=local anaesthetic; MX=low-dose local anaesthetic–opioid; OP=opioid. Compiled data are shown with 95% confidence intervals

A. Lower extremity surgery

Reference	**Congruent epidural catheter placement**	**Intra-operative epidural**	**Postoperative epidural**	**Pulmonary complications**	
				Epidural analgesia	**Opioid analgesia**
60	Yes	None	LA	1 of 7 patients[a]	3 of 9 patients
15	–	LA	OP	6 of 49 patients[e]	14 of 51 patients

B. Major abdominal surgery

Reference	**Congruent epidural catheter placement**	**Intra-operative epidural**	**Postoperative epidural**	**Pulmonary complications**	
				Epidural analgesia	**Systemic analgesia**
Epidural local anaesthetics					
75	Yes	None	LA	2 of 11 patients[a]	7 of 10 patients
60	Yes	None	LA	6 of 13 patients[a]	9 of 11 patients
1	Yes	None	LA	1 of 25 patients	5 of 25 patients
17	Yes	None	LA	0 of 15 patients[a c]	2 of 18 patients
18	Yes	LA	LA	1 of 25 patients	11 of 50 patients
29	Yes	LA	LA	2 of 60 patients	1 of 40 patients
64	No	LA	LA	0 of 24 patients[a]	3 of 24 patients
66	Yes	LA	LA	4 of 45 patients	4 of 35 patients
19	Yes	LA	LA	3 of 25 patients	2 of 25 patients
Epidural local anaesthetic–opioid mixtures					
17	Yes	None	MX	0 of 15 patients[a c]	2 of 18 patients
32	No	LA	MX	9 of 44 patients	14 of 50 patients
76	Yes	LA	MX	0 of 40 patients[d]	5 of 40 patients
36	Yes	LA	MX	21 of 78 patients[b]	23 of 75 patients
22	No	MX	MX	2 of 48 patients	2 of 51 patients
51	Yes	MX	MX	4 of 31 patients[b]	3 of 33 patients
Total EPI-LA/MX vs systemic analgesia (pneumonia and respiratory failure). References 1, 17–19, 22, 29, 32, 36, 51, 66, 76				47 of 451 patients (10.4%, 7.6–13.2%)	74 of 442 patients (16.7%, 13.3–20.2%)
Total EPI-LA/MX vs systemic analgesia with thoracic epidural analgesia (pneumonia and respiratory failure). References 1, 17–19, 29, 36, 51, 66, 76				36 of 329 patients (10.9%, 7.6–14.3%)	54 of 323 patients (16.7%, 12.6–20.8%)
Total EPI-LA/MX vs systemic analgesia (atelectasis and other not well defined pulmonary outcome). References 60, 64, 75				8 of 48 patients (16.7%, 6.1–27.2%)	19 of 45 patients (42.2%, 27.8–56.7%)

C. Major abdominal surgery

Reference	**Congruent epidural catheter placement**	**Intra-operative epidural technique**	**Postoperative epidural technique**	**Pulmonary complications**	
				Epidural analgesia	**Systemic analgesia**
67				3 of 14 patients[a]	10 of 15 patients
62	–	LA	OP	1 of 15 patients	6 of 15 patients
17	–	None	OP	0 of 18 patients[a c]	2 of 18 patients
83	–	LA	OP	3 of 28 patients	11 of 25 patients
35	–	LA	OP	19 of 74 patients[b]	15 of 72 patients
45	–	LA	OP	0 of 23 patients	5 of 41 patients
Total EPI-OP vs systemic analgesia (pneumonia and respiratory failure). References 35, 45, 62, 83				23 of 140 patients (16.4%, 10.3–22.6%)	37 of 153 patients (24.2%, 17.4–31.0%)
Total EPI-OP vs systemic analgesia (atelectasis and other not well defined pulmonary outcome). References 17, 67				3 of 32 patients (9.4%, 0.0–19.5%)	12 of 33 patients (36.4%, 20.0–53.0%)

Table 2 *Continued.*

D. Thoracic surgery

Reference	Congruent epidural placement technique	Intraoperative epidural technique	Postoperative epidural technique	Pulmonary complications	
				Epidural analgesia	Systemic analgesia
Epidural local anaesthetic or local anaesthetic–opioid					
49	Yes	LA	LA	1 of 10 patients[a, c]	1 of 10 patients
49	Yes	MX	MX	2 of 11 patients[a, c]	1 of 10 patients
4	Yes	MX	MX	1 of 25 patients[a]	0 of 25 patients
Total LA/MX vs systemic analgesia				4 of 46 patients (8.7%, 0.5–16.8%)	2 of 25 patients (8.0%, 0–18.6%)
Epidural opioid					
26	–	LA	OP	9 of 83 patients[a]	23 of 80 patients
49	–	OP	OP	3 of 12 patients[a, c]	1 of 10 patients
27	–	LA to systemic group None to epidural group	OP	7 of 58 patients[a]	27 of 71 patients
68	–	None	OP	5 of 20 patients[a]	5 of 20 patients
24	– (thoracic)	None	OP	2 of 16 patients[a, c]	3 of 16 patients
24	– (lumbar)	None	OP	4 of 16 patients[a, c]	3 of 16 patients
74	-	OP	OP	2 of 15 patients[a]	7 of 15 patients
Total EPI–opioid vs systemic analgesia				30 of 205 patients (14.6%, 9.8–19.5%)	66 of 212 patients (31.1%, 24.9–37.4%)

various surgical procedures, epidural local anaesthetics were found to reduce postoperative complications compared with epidural or systemic opioid techniques. Intercostal and intrapleural blockade and wound infiltration with local anaesthetic had no effect on pulmonary outcome.[6] Furthermore, it was demonstrated that surrogate outcome measures, such as pulmonary function, did not correlate with a clinically relevant outcome (pneumonia).[6] However, because of the limited number of studies, no distinction was made in this meta-analysis between the magnitude and location of surgery and the level of epidural blockade. Another factor that may limit the final interpretation of the effect in different operative procedures is the different definitions of pneumonia used in the various studies (see legend of Table 2).

The effects of continuous epidural analgesic techniques on pulmonary morbidity are shown in Table 2. In lower extremity surgery (Table 2A), the limited data do not allow the different epidural techniques to be separated, but overall there is a non-significant reduction from 17 of 60 patients (28.3%) to 7 of 56 patients (12.5%) in pulmonary complications by epidural analgesia compared with systemic opioid analgesia. In major abdominal and vascular surgery (Table 2B), continuous epidural local anaesthetic techniques led to a significant reduction in pulmonary complications from 16.7% to 10.4%. However, when consideration was restricted to studies in which thoracic epidural analgesia was used (which is rational in abdominal procedures), the reduction in pulmonary complications—from 16.7% to 10.9%—was not significant. Similarly, the risk of less well-defined pulmonary complications (atelectasis and others) was reduced insignificantly. Furthermore, there was only a non-significant reduction with the epidural opioid techniques (24.2% to 16.4%) (Table 2C). However, these latter data should be interpreted with caution, as the results have been influenced by the small number of studies. Thus, the study by Yeager and colleagues,[83] which was mainly a study of a continuous postoperative opioid technique, is difficult to interpret as it includes a variety of major procedures with different aetiology. In thoracic (non-cardiac) surgery, most of the epidural studies have involved a postoperative epidural opioid-based regimen, which led to a significant reduction in pulmonary morbidity from 31.1% to 14.6% (Table 2D). However, it should be emphasized that this positive effect was predominantly caused by the results of two studies from the same group.[26] [27] No difference in pulmonary outcome was observed in the small number of local anaesthetic trials in thoracic surgery (8.0% versus 8.7%) (Table 2D).

In conclusion, continuous epidural local anaesthetic or local anaesthetic–opioid mixtures have only been demonstrated to provide a reduction in postoperative pulmonary morbidity in major abdominal procedures. Epidural opioid-based regimens also reduced pulmonary morbidity in abdominal (non-significantly) and thoracic procedures (significantly), but these results were largely influenced by a few studies. More work is required to validate these conclusions, as the number of patients studied was very limited and there was considerable variation in pulmonary morbidity in the individual studies. Furthermore, definitions of pulmonary outcome often differed between these studies, which further limits interpretation and a formal meta-analysis.

Cardiac morbidity

Cardiac morbidity is a major cause of perioperative death.[50] Epidural analgesic techniques, which include local anaes-

Table 3 Effects of epidural analgesia on cardiac complications in patients undergoing major non-cardiac surgery and lower extremity vascular surgery. Complications are counted as incidents, not patients. Cardiac complications are defined as heart failure, clinically significant ischaemic events (angina, acute myocardial infarction) and/or arrhythmias. LA=epidural local anaesthetic; MX=epidural low-dose local anaesthetic–opioid; OP=epidural opioid. In one study [a], surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study [b], the type of arrhythmia was not specified. Lower extremity surgery includes vascular surgery. Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery. Major thoracic surgery includes all non-cardiac intrathoracic procedures

Reference	Congruent epidural catheter	Intra-operative epidural technique	Postoperative epidural analgesia	Number of cardiac complications with epidural analgesia	Number of cardiac complications with systemic analgesia
Lower extremity procedures					
72	Yes	LA	MX	3 of 26 patients[b]	0 of 25 patients
15	Yes	LA	OP	4 of 49 patients	8 of 51 patients
Major abdominal surgery: epidural local anaesthetic or local anaesthetic–opioid					
28	Yes	LA	LA	5 of 60 patients	5 of 40 patients
19	Yes	LA	LA	8 of 25 patients	7 of 25 patients
32	No	LA	MX	2 of 44 patients	5 of 50 patients
76	Yes	LA	MX	6 of 40 patients[a]	21 of 40 patients
22	No	MX	MX	19 of 48 patients	22 of 51 patients
9	Yes	None	MX	8 of 55 patients	9 of 59 patients
13	Yes	LA	MX	0 of 21 patients	1 of 21 patients
Total EPI-LA/MX vs systemic analgesia.				48 of 293 patients	70 of 286 patients
References 9, 13, 19, 22, 28, 32, 76				(16.4%, 12.1–20.6%)	(24.5%, 19.5–29.5%)
Total EPI-LA/MX vs systemic analgesia with thoracic epidural analgesia.				27 of 201 patients	43 of 185 patients
References 9, 13, 19, 28, 76				(13.4%, 8.7–18.1%)	(23.2%, 17.2–29.3%)
Major abdominal surgery: epidural opioid					
83	–	LA	OP	4 of 28 patients	19 of 25 patients

thetics, may reduce sympathetic responses and have a favourable effect on cardiac outcome.[48] Unfortunately, the effect of postoperative epidural analgesic techniques on cardiac complications is controversial, because of lack of the data from major studies, differences in definitions of cardiac adverse outcomes, the use of different analgesic techniques and the small number of studies investigating high-risk patients.

In lower extremity procedures (Table 3), the only study available has shown a reduction in cardiac complications with epidural opioid.[15] However, intraoperative epidural local anaesthetic was also used, which may have contributed to the reduced risk of myocardial infarction.[65] The data from major abdominal surgery (Table 3) derive mostly from the use of epidural local anaesthetic techniques, while the regimen used in the study by Yeager and colleagues[83] was predominantly based on epidural opioid analgesia (but with intra-operative local anaesthetics). However, this study is controversial as the patient population was not well defined (underlying disease and type of surgery). In another, often-cited study in a high-risk population scheduled for major surgery,[8] the group receiving postoperative epidural opioid analgesia had a lower incidence of ventricular tachycardia than the group receiving systemic opioid analgesia. However, as this study was not randomized, it was excluded from the final data analysis. The epidural regimens based on local anaesthetics led to a non-significant reduction in postoperative cardiac morbidity from 24.5% to 16.4% in major abdominal procedures. When the two studies[22 32] with inappropriate use of lumbar epidural local anaesthetic for abdominal procedures were excluded, the conclusion was not altered (non-significant reduction with thoracic epidural from 23.2% to 13.4%). The two opioid-based epidural regimens in the lower extremity and in mixed surgical procedures also led to a reduction in cardiac morbidity.[15 83] The cumulative data may therefore suggest a clinically relevant reduction in cardiac morbidity, but further data are required from well-defined surgical procedures and patients, preferably including cardiac high-risk patients, in order to reach useful and statistically valid conclusions.

Thromboembolic complications

A recent meta-analysis comparing regional anaesthesia with general anaesthesia showed that the regional anaesthetic techniques reduced postoperative thromboembolic complications and pulmonary embolism.[65] These effects may be mediated by a reduction in intraoperative blood loss, an increase in venous blood flow, decreased coagulability and increased fibrinolysis after epidural or spinal local anaesthetics.[40] As mentioned above, the overall results from the meta-analysis did not differentiate between the effects of single-dose and continuous administration of epidural analgesia. In a specific analysis of randomized studies of continuous epidural analgesic techniques, a significant reduction in thromboembolic complications (assessed by phlebography or iodine–fibrinogen scans) from 62.0% to 28.7% was found in four randomized trials in hip surgery,[21 53–55] knee surgery,[37] prostatectomy[30] and low extremity vascular surgery.[15] All of these studies except one[15] investigated postoperative epidural local anaesthetic techniques. In contrast, five randomized clinical trials in abdominal surgery, also diagnosing thromboembolic com-

Table 4 Randomized, controlled trials in which the effect of epidural analgesia on thromboembolic complications was assessed. For thromboembolic complications, we counted patients with peripheral thrombosis because additional pulmonary embolism was always combined with peripheral thrombosis. In addition, two vascular studies[15] [76] were included. We assumed that thromboembolic complications led to regrafting, which was assessed in both studies. One study[76] was a mixture of lower extremity vascular surgery and aortic surgery. In the studies shown in the upper part of the table, well-defined diagnostic procedures were applied to diagnose thromboembolic complications in all patients included in each study. When both fibrinogen scan and phlebography were used to diagnose peripheral thrombosis, the incidence of thrombosis diagnosed by fibrinogen scan was assessed. In the studies shown in the lower part of the table, no specific diagnostic procedures were mentioned or systematically performed in order to diagnose thromboembolic complications. In studies marked [a], the thromboembolic complications were non-symptomatic, or the clinical symptoms (if any) were not described. Number of clinically significant thromboses are shown within parentheses. We counted the number of patients with thromboembolic complications whenever the information was obtainable. However, as several of the above-mentioned complications may have occurred in the same patient and as most of the studies only counted the number of complications, some patients may have been counted twice. In studies marked [b], it was unclear whether all patients underwent these diagnostic procedures. Thromboembolic prophylactic treatment was mentioned inconsistently in the various studies and is not available for comparison

Reference	**Intra-operative epidural technique**	**Postoperative epidural analgesia**	**Thromboembolic complications**	
			Epidural analgesia	**Systemic analgesia**
Lower extremity surgery: systematically performed diagnostic procedures				
55	LA	LA[a]	5/15	11/15
30	LA	LA	2/17 (0/17)	11/21 (6/21)
54	LA	LA[a]	12/30	23/30
53	LA	LA[a]	21/48	38/46
21	LA	LA[a]	11/26	12/25
37	None	LA	3/17 (0/17)	13/22 (2/22)
15	LA	OP	4/49 (4/49)	22/51 (22/51)
Total lower extremity surgery	58 of 202 patients	130 of 210 patients	(28.7%, 22.5–35.0%)	(62.0%, 55.3–68.5%)
Abdominal procedures: systematically performed diagnostic procedures				
31	LA	LA	4/58 (0/60)	5/40 (2/40)
32	LA	MX[a]	10/29	9/28
28	LA	MX[a] [b]	2/30	7/40
52	LA	LA/OP[a]	8/21	9/24
62	LA	OP	0/15 (0/15)	3/15 (0/15)
Total abdominal surgery	24 of 153 patients	33 of 147 patients	(15.7%, 9.9–21.4%)	(22.4%, 15.7–29.2%)
Abdominal procedures: no systematically performed diagnostic procedures				
17	LA	LA	0/15	0/18
11	LA	LA	0/57	1/59
66	LA	LA	2/45	0/45
17	LA	MX	0/15	0/18
76	LA	MX	1/40	9/40
13	LA	MX	0/21	1/21
17	LA	OP	0/18	0/18
Thoracic surgery: no systematically performed diagnostic procedures				
49	LA	LA	0/10	0/10
49	MX	MX	0/11	0/10
49	OP	OP	0/12	0/10
Total			3 of 244 patients (1.3%, 0–2.6%)	11 of 193 patients (5.7%, 2.4–9.0%)

plications by phlebography or iodine–fibrinogen scans, found a non-significant reduction (from 22.4% to 15.7%) when systemic opioid analgesia was compared with epidural analgesic regimens. In three of these five studies[28 31 32] an epidural local anaesthetic regimen was used. Furthermore, in six randomized, controlled trials with no specific criteria for diagnosis of thromboembolic complications in major abdominal and thoracic surgery (Table 4), there was no significant difference in the incidence of thromboembolic complications (epidural analgesia 1.3%, systemic analgesia 5.7%). The discrepancy between the findings for abdominal surgery and those for lower body procedures in thromboembolic complications, with or without epidural analgesia, may be explained by the smaller effect on lower extremity blood flow, blood loss and coagulation and fibrinolysis with thoracic epidural analgesia.[40] It should be emphasized that in only one[13] of the abdominal studies was there specific emphasis on active mobilization facilitated by the improved analgesia provided by the epidural technique.

In conclusion, continuous epidural local anaesthetic reduces the risk of thromboembolic complications after lower body procedures (as observed with single-dose regional anaesthesia with local anaesthetics), whereas no significant positive effects have been observed with continuous thoracic epidural local anaesthetics after major abdominal procedures.

Gastrointestinal complications (paralytic ileus)

Postoperative paralytic ileus (PI) may last for days and prolong hospitalization and convalescence.[34] The main pathogenic factor of PI is activation of inhibitory splanchnic reflexes, which are subject to modification by thoracic

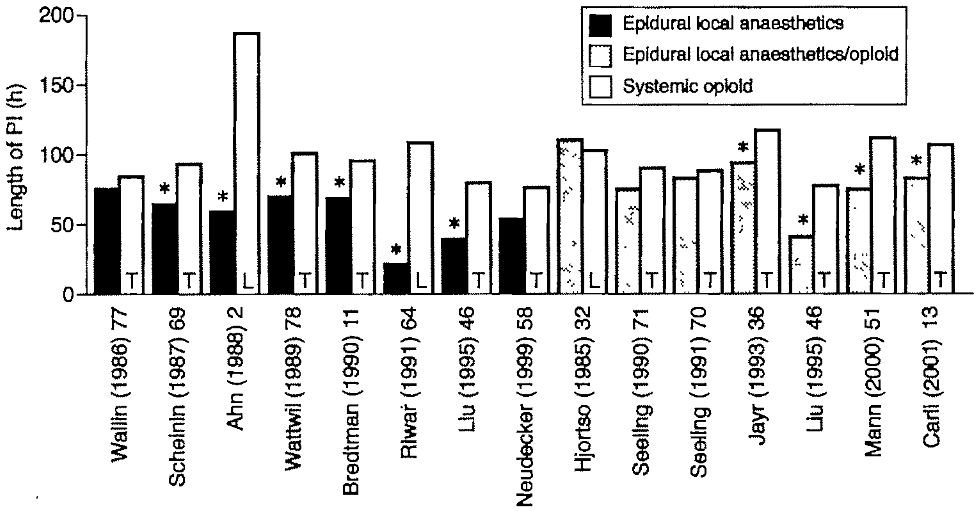

Fig 1 Effects of postoperative epidural local anaesthetic or local anaesthetic–opioid mixtures on duration of postoperative ileus (PI) in abdominal procedures. Indicators of PI are ranked in descending order (bowel movements>flatus) if more than one indicator was assessed in a study. T= thoracic epidural; L=lumbar epidural.

epidural local anaesthetics.[34 48] Accordingly, six of eight randomized clinical trials demonstrated that continuous thoracic epidural local anaesthetics reduced PI (Fig. 1).[2 11 46 58 64 69 77 78] In the two negative studies,[58 77] lack of effect was probably due to their small size, too short duration of block (24 h), or low epidural catheter insertion. In two of the three studies with inappropriate use of lumbar epidural analgesia for abdominal surgery,[2 32 64] a significant reduction in postoperative ileus was nevertheless demonstrated. When epidural local anaesthetic–opioid mixtures were compared with systemic opioid analgesia, an ileus-reducing effect was also seen in four of seven studies (Fig. 1).[13 32 36 46 51 70 71] In contrast, randomized studies have not demonstrated any reduction in ileus with an epidural opioid technique.[34]

In summary, postoperative continuous thoracic epidural local anaesthetic techniques significantly reduce PI. This effect may have major clinical implications, as it may allow early enteral nutrition, which has been demonstrated to reduce postoperative morbidity.[39] However, with a few exceptions,[13 46 58] the ileus-reducing effect of epidural local anaesthetics was not utilized to allow early oral nutrition or mobilization in these studies. There has been discussion about whether the increased gastrointestinal motility associated with epidural local anaesthetics may pose a risk to the integrity of an intestinal anastomosis. However, no risk has been demonstrated in an analysis of anastomotic dehiscence after colonic surgery using data from all published randomized studies.[33]

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction occurs in up to 20% of patients after major non-cardiac surgery and may persist in about 10% of patients 3 months after surgery.[57] The pathogenesis of postoperative cognitive dysfunction is unclear and probably multifactorial, including postoperative hypoxaemia, sleep disturbances and the use of opioids and tranquillizers. In a meta-analysis of all randomized studies comparing regional anaesthesia with general anaesthesia, no effect was found on postoperative cognitive dysfunction.[65] However, most of the studies used single-dose regional anaesthesia.

Five randomized, controlled clinical trials have examined the role of continuous postoperative epidural analgesia versus systemic opioid-based analgesia.[3 51 63 72 81] In all these studies, epidural analgesia was administered intraoperatively as an adjunct to general anaesthesia. In the largest study, in 262 patients undergoing knee surgery,[81] postoperative analgesia was not adequately standardized or described, which prevented further analysis. However, no differences were demonstrated between epidural analgesia and systemic analgesia. After prostatectomy[3] and hip surgery,[63] continuous epidural analgesia with local anaesthetic had no effect on cognitive dysfunction. Furthermore, in 51 patients undergoing knee replacement surgery, no difference in the incidence of acute delirium was found between the group receiving epidural local anaesthetic—opioid mixture and the systemic opioid group.[72] In contrast, a recent study investigating epidural low-dose bupivacaine–morphine demonstrated improved postoperative cognitive function, measured in a limited number of assessments in elderly patients after major abdominal surgery.[51]

In conclusion, the effect of postoperative continuous epidural analgesic on cognitive dysfunction is unclear. Further studies are required that also control for other pathogenic factors, such as concomitant medication, sleep disturbances and early mobilization.

Mobilization and hospital stay

The effects of epidural analgesia on postoperative mobilization have been investigated only sporadically, usually with a negative result. In one study, epidural opioid analgesia improved mobilization in obese patients undergoing gastroplasty.[62] The data from the use of continuous epidural local anaesthetic techniques in major orthopaedic procedures are controversial. Although one study demonstrated limited improvement in rehabilitation after knee replacement, hospital stay was not improved.[80] However, postoperative analgesia was not standardized in this study, although most patients randomized to epidural anaesthesia also received postoperative epidural analgesia. In one study,[12] the stay in the rehabilitation centre was reduced after continuous epidural analgesia, but the length of stay was substantial (about 40 days in total), which is different from common practice in most studies. In another study in knee and hip surgery, no difference was found in hours of daily mobilization between epidural local anaesthetic–opioid mixture and systemic opioid.[56] Furthermore, low-dose local anaesthetic–opioid epidural analgesia did not result in any improvement in rehabilitation measures in 51 patients scheduled for knee replacement surgery.[72]

The effect of epidural analgesic techniques on postoperative hospital stay, as a general indication of morbidity and mobilization is shown in Table 5. It appears that the improved pain relief given by epidural analgesic techniques (local anaesthetics, local anaesthetic–opioid mixtures, opioids alone) has no significant effect on hospital stay. These findings differ from the demonstrated positive effects in some procedures on paralytic ileus, pulmonary, cardiac and thromboembolic outcome after the use of epidural analgesia. However, as discussed below, it should be emphasized that hospital stay may be a poor outcome measure as it depends on many factors other than pain relief (e.g. use of drains, catheters, traditions, restrictions, reimbursement policy). The effect of improved pain relief by epidural analgesia may be obtunded by such factors.[39] This is supported by the finding that discharge criteria were obtained earlier in patients receiving epidural analgesia[46] but were not translated into a shorter hospital stay. Also, other studies have shown a discrepancy between achievement of discharge criteria and actual hospital stay.[47][82] Therefore, in order to demonstrate a potential reduction in hospital stay by the more costly continuous epidural analgesic techniques, the improved pain relief has to be integrated into a multimodal rehabilitation programme.[39]

Table 5 Effects of epidural analgesia on hospital stay in days. Lower extremity surgery includes vascular surgery, hip surgery and knee surgery. Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery. Major thoracic surgery includes all major non-cardiac thoracic procedures. LA=epidural local anaesthetic; MX=epidural low-dose local anaesthetic–opioid; OP=epidural opioid. Studies in which several types of epidural analgesia were evaluated (against the same control group) are marked ^{a}. In one study ^{b}, surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study ^{c}, hospital stay was reported separately for the two subgroups of the study: knee (first line) and hip surgery (second line). *$P<0.05$ in the individual study

Reference	Epidural analgesia			Systemic analgesia
	LA	MX	OP	
Lower extremity procedures and prostatectomy				
60	4, 7			8, 9
82	19			22
56		12^{c}		13
56		9^{c}		9
15			9	10
Major abdominal surgery				
Epidural local anaesthetics or local anaesthetic–opioid mixture				
60	4.8			5, 8
78	7.7			7.4
11	19.9			18.9
64	13.5			14.5
19	16			16
46	4.2^{a}			5,1
58	10			8
71		19		18
76		10.7^{b}		11.7
70		19		19
36		18		16
46		8.3^{a}		5.1
9		16.3		13.9
51		10.5		11.5
13		8.5		7.3
Total LA/MX vs systemic analgesia		12.4 days		12.4 days
Epidural opioid				
62			7.1*	9.0
83			11.4*	15.8
46			5.4^{a}	5.1
Major thoracic surgery				
4		9.5		11.1
73			9.9	9.6
24			11.1^{a} * (thoracic group)	15.6
24			14.4^{a} * (lumbar group)	15.6
74			15.5	17.1

Integration of postoperative pain relief and rehabilitation

In recent years, postoperative pain treatment has been optimized, especially after introduction of acute pain services. Furthermore, extensive data have demonstrated beneficial physiological effects of efficient analgesia on several organ systems. It is therefore surprising and somewhat disappointing that the overall effect of pain-relieving techniques on postoperative morbidity has so far been rather small or non-demonstrable by statistical analysis. There are several explanations for this. First, most studies have been small, with insignificant power (small number of patients and outcome) to demonstrate advantageous effects. Secondly, it is unlikely that a unimodal treatment (effective pain relief) for a complex problem such as perioperative morbidity will provide major improvements in outcome. Instead, a multimodal effort has been proposed to include effective control of postoperative pain, thereby allowing early mobilization and enforcement of an early oral feeding programme, together with the stress-reducing effect of regional anaesthetic techniques.[39] Also, improved information for the patient well in advance of surgery is necessary.

Although the concept of multimodal postoperative rehabilitation seems rational and simple, progress has been slow.[39 41] The most plausible explanation is that a successful multimodal rehabilitation programme requires the reorganization of peri-operative care, with increased collaboration between the patient, anaesthetist (acute pain service), surgical nurse and surgeon. Furthermore, major efforts must be made for educational programmes, with emphasis on peri-operative pathophysiology, as well as a revision of traditional postoperative care programmes with drains, gastrointestinal tubes, catheters, restrictions, etc. So far, preliminary experience from a variety of surgical procedures has shown such a collaborative effort to be extremely successful in reducing hospital stay and morbidity.[7 39 41] To improve the rate of progress and to quantify the potential advantageous effects of analgesic techniques on postoperative outcome, a detailed analysis must be made of the various factors that may limit early recovery after each individual procedure, and be responsible for hospitalization on a given day. A key factor in the success of a multimodal rehabilitation programme is the development of daily nurse care programmes with an emphasis on rehabilitation[7] and the expansion of the traditional acute pain service into a collaborative effort in functional recovery.

In summary, postoperative pain relief continues to demand our attention, but further progress is needed if we are to optimize functional (dynamic) pain relief and to demonstrate clinically significant advantages of pain relief for surgical outcome. The concept of a multimodal postoperative rehabilitation programme in which pain relief is a key factor is a major task for the future. However, such efforts will undoubtedly lead to major improvements in outcome, provided that perioperative care is adjusted to derive the benefits of the physiological effects of good pain relief.

References

1 Addison NV, Brear FA, Budd K, Whittaker M. Epidural analgesia following cholecystectomy. *Br J Surg* 1974; **61**: 850–2

2 Ahn H, Bronge A, Johànsson K, Ygge H, Lindhagen J. Effect of continuous postoperative epidural analgesia on intestinal motility. *Br J Surg* 1988; **75**: 1176–8

3 Asbjorn J, Jakobsen BW, Pilegaard HK, Blom L, Ostergaard A, Brandt MR. Mental function in elderly men after surgery during epidural analgesia. *Acta Anaesthesiol Scand* 1989; **33**: 369–73

4 Azad SC, Groh J, Beyer A, Schneck D, Dreher E, Peter K. Continuous epidural analgesia versus patient controlled intravenous analgesia for postthoracotomy pain. *Acute Pain* 2000; **3**: 84–93

5 Ballantyne JC, Carr DB, Chalmers TC, Dear KB, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. *J Clin Anesth* 1993; **5**: 182–93

6 Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; **86**: 598–612

7 Basse L, Hjort JD, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; **232**: 51–7

8 Beattie WS, Buckley DN, Forrest JB. Epidural morphine reduces the risk of postoperative myocardial ischaemia in patients with cardiac risk factors. *Can J Anaesth* 1993; **40**: 532–41

9 Bois S, Couture P, Boudreault D, *et al.* Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. *Anesth Analg* 1997; **85**: 1233–9

10 Boulanger A, Choiniere M, Roy D, Boure B, Chartrand D, Choquette R, Rousseau P. Comparison between patient-controlled analgesia and intramuscular meperidine after thoracotomy. *Can J Anaesth* 1993; **40**: 409–15

11 Bredtmann RD, Herden HN, Teichmann W, *et al.* Epidural analgesia in colonic surgery: results of a randomized prospective study. *Br J Surg* 1990; **77**: 638–42

12 Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; **91**: 8–15

13 Carli F, Trudel J, Belliveau P. Return of bowel function after thoracic epidural anesthesia. *Dis Colon Rectum* 2001. In press

14 Chan VW, Chung F, McQuestion M, Gomez M. Impact of patient-controlled analgesia on required nursing time and duration of postoperative recovery. *Reg Anesth* 1995; **20**: 506–14

15 Christopherson R, Beattie C, Frank SM, *et al.* Perioperative Ischemia Randomized Anesthesia Trial Study Group. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. *Anesthesiology* 1993; **79**: 422–34

16 Colwell CW Jr, Morris BA. Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopaedic procedure. *J Bone Joint Surg Am Vol* 1995; **77**: 726–33

17 Cullen ML, Staren ED, El-Ganzouri A, Logas WG, Ivankovich AD, Economou SG. Continuous epidural infusion for analgesia after major abdominal operations: a randomized, prospective, double-blind study. *Surgery* 1985; **98**: 718–28

18 Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. *Br J Surg* 1985; **72**: 495–8

19 Davies MJ, Silbert BS, Mooney PJ, Dysart RH, Meads AC. Combined epidural and general anaesthesia versus general anaesthesia for abdominal aortic surgery: a prospective randomised trial. *Anaesth Intens Care* 1993; **21**: 790–4

20 Egbert AM, Parks LH, Short LM, Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med* 1990; **150**: 1897–903

21 Fredin H, Rosberg B. Anaesthetic techniques and thromboembolism in total hip arthroplasty. *Eur J Anaesthesiol* 1986; **3**: 273–81

22 Garnett RL, MacIntyre A, Lindsay P, *et al.* Perioperative ischaemia in aortic surgery: combined epidural/general anaesthesia and epidural analgesia vs general anaesthesia and i.v. analgesia. *Can J Anaesth* 1996; **43**: 769–77

23 Grass JA. The role of epidural anesthesia and analgesia in postoperative outcome. *Anesthesiol Clin N Am* 2000; **18**: 407–28

24 Guinard JP, Mavrocordatos P, Chiolero R, Carpenter RL. A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. *Anesthesiology* 1992; **77**: 1108–15

25 Gust R, Pecher S, Gust A, Hoffmann V, Bohrer H, Martin E. Effect of patient-controlled analgesia on pulmonary complications after coronary artery bypass grafting. *Crit Care Med* 1999; **27**: 2218–23

26 Hasenbos M, van Egmond J, Gielen M, Crul JF. Postoperative analgesia by epidural versus intramuscular nicomorphine after thoracotomy. Part II. *Acta Anaesthesiol Scand* 1985; **29**: 577–82

27 Hasenbos M, van Egmond J, Gielen M, Crul JF. Postoperative analgesia by high thoracic epidural versus intramuscular nicomorphine after thoracotomy. Part III. The effects of per- and postoperative analgesia on morbidity. *Acta Anaesthesiol Scand* 1987; **31**: 608–15

28 Hendolin H, Lahtinen J, Lansimies E, Tuppurainen T. The effect of thoracic epidural analgesia on postoperative stress and morbidity. *Ann Chir Gynaecol* 1987; **76**: 234–40

29 Hendolin H, Lahtinen J, Lansimies E, Tuppurainen T, Partanen K. The effect of thoracic epidural analgesia on respiratory function after cholecystectomy. *Acta Anaesthesiol Scand* 1987; **31**: 645–51

30 Hendolin H, Mattila MA, Poikolainen E. The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy. *Acta Chir Scand* 1981; **147**: 425–9

31 Hendolin H, Tuppurainen T, Lahtinen J. Thoracic epidural analgesia and deep vein thrombosis in cholecystectomized patients. *Acta Chir Scand* 1982; **148**: 405–9

32 Hjortso NC, Neumann P, Frosig F, *et al.* A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* 1985; **29**: 790–6

33 Holte K, Kehlet H. Epidural anesthesia and risk of anastomotic leakage. *Reg Anesth Pain Med* 2001; **26**: 111–17

34 Holte K, Kehlet H. Postoperative ileus—a preventable event? *Br J Surg* 2000; **87**: 1480–93

35 Jayr C, Mollie A, Bourgain JL, *et al.* Postoperative pulmonary complications: general anesthesia with postoperative parenteral morphine compared with epidural analgesia. *Surgery* 1988; **104**: 57–63

36 Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain JL. Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. *Anesthesiology* 1993; **78**: 666–76

37 Jorgensen LN, Rasmussen LS, Nielsen PT, Leffers A, Albrecht-Beste E. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. *Br J Anaesth* 1991; **66**: 8–12

38 Kehlet H. Postoperative pain relief—what is the issue? *Br J Anaesth* 1994; **72**: 375–8

39 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17

40 Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 3rd Edn. Philadelphia: Lippincott-Raven, 1998; 129–71

41 Kehlet H. Acute pain control and accelerated postoperative surgical recovery. *Surg Clin N Am* 1999; **79**: 431–45

42 Kehlet H, Rung GW, Callesen T. Postoperative opioid analgesia: time for a reconsideration? *J Clin Anesth* 1996; **8**: 441–5

43 Kehlet H, Werner M, Perkins F. Balanced analgesia: what is it and what are its advantages in postoperative pain? *Drugs* 1999; **58**: 793–7

44 Kenady DE, Wilson JF, Schwartz RW, Bannon CL, Wermeling D. A randomized comparison of patient-controlled versus standard analgesic requirements in patients undergoing cholecystectomy. *Surg Gynecol Obstet* 1992; **174**: 216–20

45 Kilbride MJ, Senagore AJ, Mazier WP, Ferguson C, Ufkes T. Epidural analgesia. *Surg Gynecol Obstet* 1992; **174**: 137–40

46 Liu S, Carpenter RL, Mackey DC, *et al.* Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995; **83**: 757–65

47 Liu S, Carpenter RL, Mulroy MF, *et al.* Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. *Anesthesiology* 1995; **82**: 682–8

48 Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; **82**: 1474–506

49 Logas WG, El-Baz N, El-Ganzouri A, *et al.* Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. *Anesthesiology* 1987; **67**: 787–91

50 Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; **72**: 153–84

51 Mann C, Pouzeratte Y, Boccara G, *et al.* Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000; **92**: 433–41

52 Mellbring G, Dahlgren S, Reiz S, Sunnegardh O. Thromboembolic complications after major abdominal surgery: effect of thoracic epidural analgesia. *Acta Chir Scand* 1983; **149**: 263–8

53 Modig J, Maripuu E, Sahlstedt B. Thromboembolism following total hip replacement—a prospective investigation of 94 patients with emphasis on the efficacy of lumbar epidural anesthesia in prophylaxis. *Reg Anesth* 1986; **11**: 72–9

54 Modig J, Borg T, Karlstrom G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. *Anesth Analg* 1983; **62**: 174–80

55 Modig J, Hjelmstedt A, Sahlstedt B, Maripuu E. Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. *Acta Chir Scand* 1981; **147**: 125–30

56 Moiniche S, Hjortso NC, Hansen BL, *et al.* The effect of balanced analgesia on early convalescence after major orthopaedic surgery. *Acta Anaesthesiol Scand* 1994; **38**: 328–35

57 Moller JT, Cluitmans P, Rasmussen LS, *et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. *Lancet* 1998; **351**: 857–61

58 Neudecker J, Schwenk W, Junghans T, Pietsch S, Bohm B, Muller JM. Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection. *Br J Surg* 1999; **86**: 1292–5

59 Nitschke LF, Schlosser CT, Berg RL, Selthafner JV, Wengert TJ, Avecilla CS. Does patient-controlled analgesia achieve better control of pain and fewer adverse effects than intramuscular analgesia? A prospective randomized trial. *Arch Surg* 1996; **131**: 417–23

60 Pflug AE, Murphy TM, Butler SH, Tucker GT. The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. *Anesthesiology* 1974; **41**: 8–17

61 Power I, Barratt S. Analgesic agents for the postoperative period. Nonopioids. *Surg Clin N Am* 1999; **79**: 275–95

62 Rawal N, Sjostrand U, Christoffersson E, Dahlstrom B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. *Anesth Analg* 1984; **63**: 583–92

63 Riis J, Lomholt B, Haxholdt O, *et al.* Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. *Acta Anaesthesiol Scand* 1983; **27**: 44–9

64 Riwar A, Schar B, Grotzinger U. Effect of continuous postoperative analgesia with peridural bupivacaine on intestinal motility following colorectal resection. *Helv Chir Acta* 1992; **58**: 729–33

65 Rodgers A, Walker N, Schug S, *et al.* Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia. Results from overview of randomised trials. *Br Med J* 2000; **321**: 1493–7

66 Ryan P, Schweitzer SA, Woods RJ. Effect of epidural and general anaesthesia compared with general anaesthesia alone in large bowel anastomoses. A prospective study. *Eur J Surg* 1992; **158**: 45–9

67 Rybro L, Schurizek BA, Petersen TK, Wernberg M. Postoperative analgesia and lung function: a comparison of intramuscular with epidural morphine. *Acta Anaesthesiol Scand* 1982; **26**: 514–8

68 Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. *Anesthesiology* 1991; **75**: 790–5

69 Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. *Acta Anaesthesiol Scand* 1987; **31**: 161–4

70 Seeling W, Bothner U, Eifert B, *et al.* Patient-controlled analgesia versus epidural analgesia using bupivacaine or morphine following major abdominal surgery. No difference in postoperative morbidity. *Anaesthesist* 1991; **40**: 614–23

71 Seeling W, Bruckmooser KP, Hufner C, Kneitinger E, Rigg C, Rockemann M. No reduction in postoperative complications by the use of catheterized epidural analgesia following major abdominal surgery. *Anaesthesist* 1990; **39**: 33–40

72 Sharrock NE, Urquhart BL, Ganz S, Williams-Russo PG. Epidural infusions of bupivacaine and fentanyl do not improve rehabilitation following one-stage bilateral total knee arthroplasty. *Ann Acad Med Singapore* 1994; **23** (6 Suppl): 3–9

73 Shulman M, Sandler AN, Bradley JW, Young PS, Brebner J. Postthoracotomy pain and pulmonary function following epidural and systemic morphine. *Anesthesiology* 1984; **61**: 569–75

74 Slinger P, Shennib H, Wilson S. Postthoracotomy pulmonary function: a comparison of epidural versus intravenous meperidine infusions. *J Cardiothorac Vasc Anesth* 1995; **9**: 128–34

75 Spence AA, Smith G. Postoperative analgesia and lung function: a comparison of morphine with extradural block. *Br J Anaesth* 1971; **43**: 144–8

76 Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 1991; **73**: 696–704

77 Wallin G, Cassuto J, Hogstrom S, Rimback G, Faxen A, Tollesson PO. Failure of epidural anesthesia to prevent postoperative paralytic ileus. *Anesthesiology* 1986; **65**: 292–7

78 Wattwil M, Thoren T, Hennerdal S, Garvill JE. Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. *Anesth Analg* 1989; **68**: 353–8

79 Wheatley RG, Shug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* 2001; **87**: 47–61

80 Williams-Russo P, Sharrock NE, *et al.* Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. *Clin Orthop Rel Res* 1996; 199–208

81 Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *J Am Med Assoc* 1995; **274**: 44–50

82 Wulf H, Biscoping J, Beland B, Bachmann-Mennenga B, Motsch J. Ropivacaine epidural anesthesia and analgesia versus general anesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. Ropivacaine Hip Replacement Multicenter Study Group. *Anesth Analg* 1999; **89**: 111–6

83 Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology* 1987; **66**: 729–36

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Analgesia for day-case surgery

N. Rawal

Department of Anaesthesiology and Intensive Care, Örebro Medical Centre Hospital, S-701 85 Örebro, Sweden

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Recent advances in anaesthetic and surgical techniques, along with escalating healthcare costs, have resulted in an ever-increasing number of surgical procedures being performed on a day-case basis world-wide. The cost-effectiveness of day-case surgery is well recognized. Day-case surgery constituted 60–70% of all surgery performed in North America in the 1990s,[22] but in other parts of the world the numbers are lower. However, as outcome data become available confirming the safety of day-case surgery, it is anticipated that even more procedures will be performed on a day-case basis. Recent surgical advances include the use of endoscopic approaches for procedures such as micro-discectomy, tubal interrupt and carpal tunnel release. Major day-care surgery procedures (e.g. knee and shoulder reconstructions, laparoscopic-assisted vaginal hysterectomies, gastric fundoplications, splenectomies and adrenalectomies) are being performed at many centres. Even pulmonary lobectomy, prostatectomy, carotid endarterectomy and minor craniectomy procedures are being performed on a same-day (or 23 h admission) basis.[94] Major advances in anaesthetic techniques include the use of anaesthetic agents of short duration and increasing use of regional anaesthetic techniques. It is expected that the number, diversity and complexity of operations performed in the outpatient setting will continue to increase.

Most day-case surgery procedures are associated with relatively minor surgical trauma, so discharge of these patients frequently depends on recovery from anaesthesia. Top priorities for successful outpatient surgery are the four 'A's: alertness, ambulation, analgesia and alimentation. Excessive fatigue, nausea, vomiting or unrelieved pain will delay discharge; these symptoms are the most common reasons for unanticipated hospital admission. Since the proportion of surgery done on an outpatient basis is increasing, and since early discharge and patient satisfaction are important goals, pain management is receiving greater attention.

Rapid recovery after the use of new, short-acting anaesthetic agents has led to the concept of fast-tracking and by-passing the post-anaesthetic care unit (PACU).[5] However, the success of fast-tracking will depend to a considerable extent on effective postoperative pain management routines with simple methods such as oral analgesics. The potential cost saving of outpatient surgery may be negated by unanticipated hospital admission for poorly treated pain.[30] In this review, the terms 'ambulatory surgery', 'day-case surgery' and 'out-patient surgery' are used synonymously to indicate that the patient is discharged on the day of surgery without overnight hospital stay.

Severity of pain after day-case surgery

The problem of postoperative pain after discharge has generally been poorly studied.[22] Postoperative pain is one of the most common complaints after surgery and continues to be a challenge for anaesthetists. Contrary to the common belief that day surgery is followed by mild pain, recent studies have shown that under-treatment of pain is common. About 30–40% of discharged outpatients may suffer from moderate to severe pain during the first 24–48 h.[12 74] This pain decreases with time but may be severe enough to interfere with sleep and daily functioning.[29 79] Lengthy surgical procedures and certain types of operation (orthopaedic, urological, anorectal, hernia repair, breast augmentation, laparoscopic cholecystectomy, ENT, dental) tend to be associated with severe pain and therefore require more analgesia.[12 43 74]

As in adults, most studies of analgesia in paediatric day-case surgery have focused on the immediate postoperative course and largely ignored the risk of severe pain at home, when it becomes the responsibility of the parent.[96] Studies have shown that more than half of children experience clinically significant pain after discharge.[29 44 50] Despite the high frequency of under-treated postoperative pain, the overwhelming majority of patients express satisfaction with

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pain control.[12 74] Patient satisfaction regarding postoperative analgesia is a complex issue. Satisfaction ratings are often related to psychosocial aspects of care such as communication rather than to technical aspects. Several factors may account for the low level of dissatisfaction in spite of moderate to severe pain, including poor follow-up of patients, reluctance of patients to report postoperative complications, effect of memory on recalling past experience of pain and acceptance of pain as an inevitable consequence of surgery.[12]

Impact of pain after day-case surgery

Severe postoperative pain causes extreme discomfort, sleep deprivation and suffering. Along with postoperative nausea and vomiting (PONV), it is the main cause of delayed discharge, contact with the hospital after discharge, unanticipated hospital admission[30] and increased costs. Pain after day-case surgery may last several days and can have implications for return to work and for community health services. Currently, the majority of patients undergoing day-case surgery are healthy. However, elderly patients and those with concurrent disease are increasingly being included. The physiological effects of pain may be particularly harmful in patients with ischaemic heart disease or chronic respiratory problems.

The intensity of acute postoperative pain may be important for predicting the development of chronic pain after leg amputation, breast surgery and thoracotomy.[47] In day-case surgery, chronic pain is a significant problem after open groin hernia repair; the reported incidence varies from 0 to 12%. The intensity of early postoperative pain may be an important predictor of the development of chronic pain.[18]

Changes in children's behaviour have been seen after both day-case and inpatient surgery. The changes are mostly transient but in some children they persist for several weeks, months or even years. A recent multicentre survey showed a 47% incidence of problematical behavioural changes; the main predictors were age (highest incidence in children <3 years of age), pain at home and a previous difficult experience of healthcare.[52] The authors emphasized the importance of effective prevention and treatment of pain. postoperative pain also seems to be a clear predictor of PONV in children.[53]

Choice of anaesthetic technique and peri-operative analgesia

Safety, rapid recovery and minimal postoperative problems are essential in selecting surgical procedures and anaesthesia techniques for day-case surgery. The choice of anaesthetic technique can affect postoperative morbidity at home.[53] Several new drugs have significant advantages in terms of rapid onset, excellent analgesia and amnesia, good surgical conditions and early recovery. These drugs include sedative–hypnotics such as propofol, analgesics such as remifentanil, alfentanil, ketorolac and tenoxicam, muscle relaxants such as mivacurium, rocuronium, rapacuronium and inhalational agents such as desflurane and sevoflurane. These inhalation agents provide rapid and smooth induction, quick adjustments during maintenance and rapid recovery with few side-effects.

The nature, technique, extent and duration (>90 min) of surgery and the anaesthetic technique affect the incidence of postoperative morbidity at home.[22 38 53] Asking the surgeon to decompress the abdomen rigorously after laparoscopic sterilization reduces the need for postoperative opioids.[24] Gas-less and abdominal wall lift techniques reduce the incidence of PONV.[49] Patients undergoing laparoscopic, orthopaedic or general surgery are at a much greater risk of developing persistent symptoms. Certain drugs and anaesthetic techniques are similarly associated with a greater incidence of morbidity.[38] The risk of postoperative sore throat can be reduced by using the laryngeal mask airway (LMA[†]) rather than endotracheal intubation.[10] Succinylcholine may not be a suitable choice for day-case patients, because myalgias associated with its use may delay the resumption of normal activity. Day-case surgery patients are said to be at greater risk of succinylcholine-induced postoperative myalgia than hospitalized patients. The reported incidence of succinylcholine-induced myalgia varies among studies, from 45% to 85%. Pre-treatment with small doses of a non-depolarizing muscle relaxant before succinylcholine administration has been reported to minimize postoperative myalgia. However, despite this intervention, various incidences of myalgia, ranging from 20% to 70%, have been reported.[60] In children, PONV increases, even after a single dose of morphine,[93] and decreases after administration of propofol.[11] The use of regional blocks[57] or non-steroidal anti-inflammatory drugs (NSAIDs)[59] during anaesthesia has reduced the need for postoperative opioids, so their value may be not only in improvement of pain control but also in the reduction of PONV.[53]

The role of opioids in day-case surgery is controversial because of their well-known side-effects, especially nausea and vomiting. At equi-analgesic doses, the emetic effects of all opioids appear to be similar. It is emphasized that pain itself is a major cause of nausea and vomiting and opioids may be anti-emetic when given to relieve pain.[2] Although patients who receive an opioid are more likely to experience PONV, average recovery times are not significantly prolonged by the use of intra-operative opioids *per se.* Several studies have demonstrated early ambulation and discharge after fentanyl or alfentanil-based anaesthetic techniques.[101] However, there is good evidence that avoidance of opioids virtually abolishes the postoperative complaints of nausea and vomiting that preclude oral intake of fluids after surgery. The ultra-short-acting opioid, remifentanil, is associated

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[†] LMA® is the property of Intavent Limited.

Table 1 Advantages of local/regional anaesthesia (adapted from reference 81, with permission)

- Advantages to patient
  - avoidance of general anaesthetic with its related complications
  - minimal incidence of nausea and vomiting
  - improved post-operative pain relief
  - shortened recovery room time (can by-pass first-stage recovery)
  - ability to communicate with staff during surgery
  - ability to observe the procedure (arthroscopy)
  - earlier mobilization including immediate physiotherapy
- Advantages to surgeon
  - enables accurate assessment of function before end of surgery
  - allows discussion of operative findings and treatment options at surgery
- Advantages for institution
  - options of direct transfer to second-stage recovery
  - shortens patient's time in recovery room
  - reduces post-operative nursing requirements
  - fewer hospital admissions (shoulder surgery, breast augmentation surgery)
  - overall reduction in facility costs?

Table 2 Disadvantages of local/regional anaesthesia (adapted from reference 81, with permission)

- Takes longer because of:
  - discussion with patient
  - block procedure
  - onset time
  - gentle tissue handling
  - incomplete block necessitating supplementation or conversion to general anaesthetic
- Requires surgeon and patient co-operation
- Risk of post-spinal headache (spinal, CSE)
- Prolonged regional block may result in urinary retention and delayed discharge (central blocks)

with a predictable and rapid recovery that is relatively independent of the duration of infusion. However, remifentanil has a limited role in day-case surgery because its advantages of rapid postoperative recovery and no respiratory depression are negated by the requirement for a longer-acting opioid or alternative analgesic as soon as the remifentanil infusion is stopped. To quote from a recent editorial by Leach, 'There seems little logic in using a drug such as remifentanil intraoperatively to suppress the surgical response to painful stimulus, only to allow the patient to regain his senses, acknowledge that pain is severe and then obtund consciousness once more with large doses of a long-acting opioid'.[54] Furthermore, a recent study showed that intraoperative remifentanil can cause acute opioid tolerance leading to increased postoperative pain and opioid consumption.[33]

With modern general anaesthetic techniques, recovery after surgery can be both rapid and complete. However, in many day-care patients, regional anaesthetic techniques might be preferable. Regional anaesthesia can reduce or avoid the hazards and discomforts of general anaesthesia, including sore throat, airway trauma and muscle pain. Regional anaesthesia, whether by epidural, spinal, peripheral nerve blocks or field block techniques, offers a number of advantages to outpatients undergoing surgery. These techniques provide analgesia without sedation, earlier discharge and prolonged postoperative analgesia. Local or regional anaesthesia can be used alone, in combination with sedation techniques or as part of balanced analgesia with general anaesthesia. Decreased requirements for opioids reduce the incidence of postoperative nausea (Table 1).

A controversial issue in day surgery is whether regional anaesthesia offers significant benefits over general anaesthesia for ambulatory surgery. Published data are conflicting. However, the indications for regional anaesthesia vary from one institution to another.[81] All general and regional anaesthesia techniques have advantages and disadvantages. Thus, in a comparative study of spinal, epidural and propofol anaesthesia for knee arthroscopy, propofol anaesthesia was associated with shortest stay in the operating room but greatest postoperative pain and drug costs. Mepivacaine epidural block resulted in the longest stay and most prolonged postoperative analgesia. Spinal anaesthesia was the least expensive but one patient (3.3%) developed post-spinal headache.[25] Acceptance of the technique by surgeon and patient, and the expertise of the anaesthesiologist, are crucial. It is essential that each unit audits its own complication rates, recovery room times and patient opinions to determine the relevance of regional or general anaesthesia. Day surgery performed under local anaesthesia is often the simplest, safest and cheapest. It is surprising how little sedation patients require if the atmosphere is conducive and the surgeon handles the tissues gently.[38 81] Of particular importance is the ability of regional anaesthesia to provide a predictable intra- and postoperative course, thus aiding a smooth transition from surgery to recovery with anticipated early discharge. This is in contrast to the use of general anaesthesia with the associated risks of delayed discharge because of complications, particularly nausea, vomiting and pain. Indeed, unanticipated admission for these complications is almost exclusively a problem in patients receiving general anaesthesia.[81]

Regional anaesthesia does have some disadvantages (Table 2). It may take longer and it requires active co-operation of patient and surgeon. Induction may be associated with minor discomfort and there is a risk of complications specific to each block and to the local anaesthetic drug used. Furthermore, not all patients are suitable for regional anaesthesia. Difficulties in performing the block and movement during surgery can be a problem in the very anxious patient. Heavy sedation in such patients may negate the positive aspects of regional anaesthesia. If the block fails, the surgeon may be able to supplement with additional local anaesthetic and the anaesthetist must be on stand-by to convert to general anaesthesia immediately.[81]

Day-case regional anaesthesia for perioperative pain

A number of regional anaesthetic techniques can be used for day-case surgery. These techniques involve little physio-

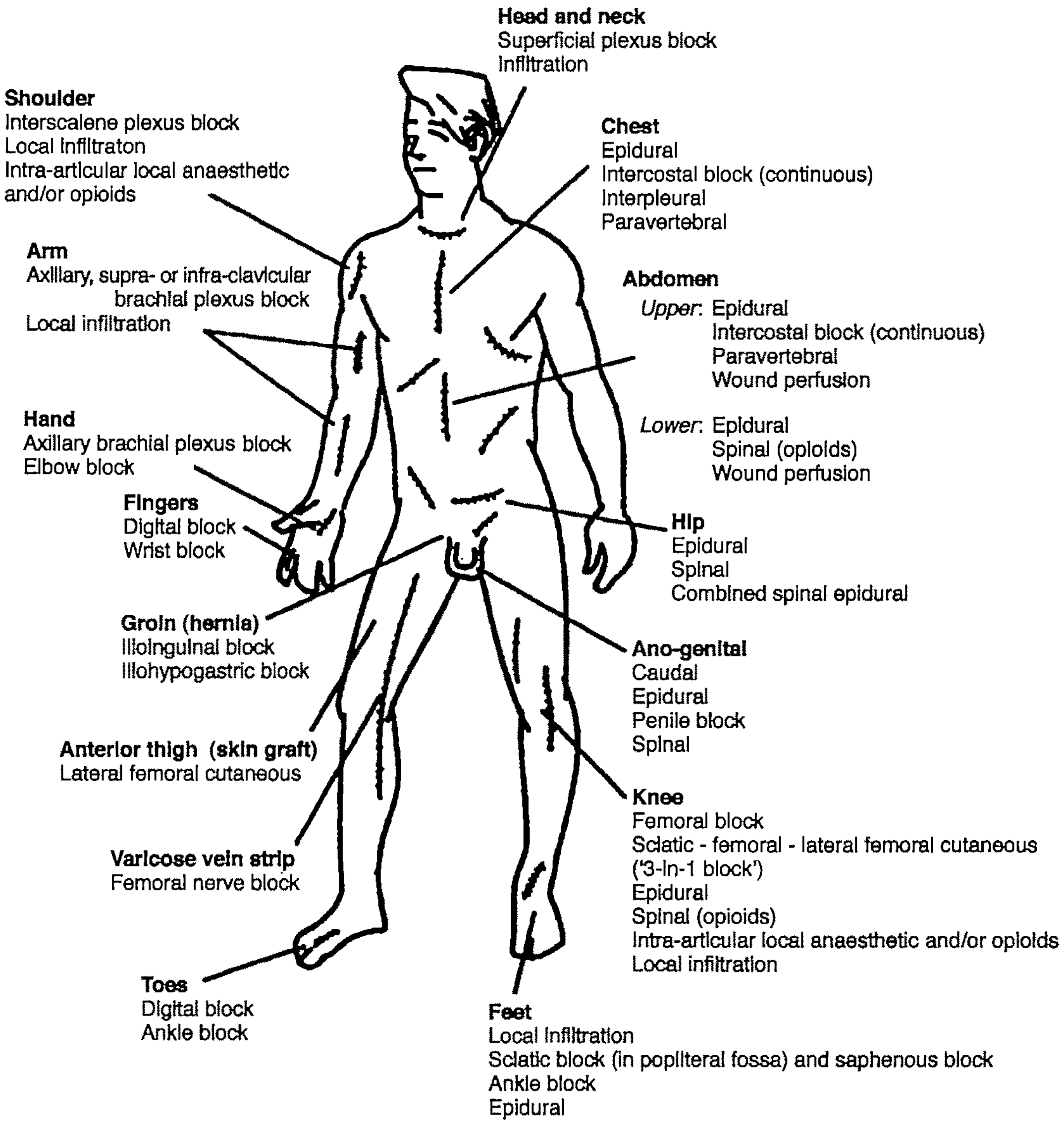

Fig 1 Possible peripheral nerve blocks for surgery and postoperative analgesia.

logical trespass, compared with general anaesthesia, and so they are particularly suited to the ever-growing population of high-risk elderly patients presenting for day-case procedures. At completion of surgery, infiltration of the wound using a long-acting local anaesthetic (e.g. 0.25% bupivacaine) provides prolonged postoperative analgesia. For ocular surgery, peribulbar, retrobulbar or topical blocks can be performed safely, effectively and with few complications.

In children, the use of regional anaesthesia techniques before the start of surgery (but after the child has been put to sleep) will reduce the requirements for general anaesthetic drugs during surgery, which may result in a more rapid recovery, less nausea and vomiting, and earlier alimentation and discharge. Caudal block is easy to perform and provides excellent analgesia for perineal or inguinal surgery. Sympathetic effects on the circulatory system are rare. Blocks may be performed on the ilioinguinal nerve, iliohypogastric nerve, the dorsal nerve of the penis, the brachial plexus, femoral nerve or digital nerves. Ring blocks of the wrist or ankle and local infiltration are simple and effective.

Intravenous regional anaesthesia

Intravenous regional anaesthesia (IVRA) is one of the most common regional techniques world-wide.[37 69] It is very easy to perform: the only technical skill necessary is the ability to perform venipuncture (although skill in resuscitation is also required if complications occur). IVRA is most suitable for short duration (<45–60 min) surgical procedures in distal extremities (forearm, hand, ankle and foot). Good surgical anaesthesia can be achieved rapidly after the injection of local anaesthetic and recovery is fast after the release of the tourniquet. No other regional anaesthetic technique provides such a control over the onset, duration and recovery of block. The published success rates range from 94% to 100%. Adjuvants such as opioids, NSAIDs and muscle relaxants have been used to improve the quality of block and postoperative analgesia, but the results are generally unimpressive. The main problems of the technique are related to the requirement for a tourniquet, and include restricted area of anaesthesia, pain associated with the tourniquet, and risk of local anaesthetic toxicity due to accidental release of the tourniquet. Some recent studies suggest that the use of ropivacaine may provide prolonged postoperative analgesia.[8 21] Although ropivacaine is less toxic than bupivacaine, its use is not recommended for IVRA because it is much more toxic than the commonly used prilocaine and chloroprocaine.[37 72]

Peripheral nerve blocks

Peripheral nerve blocks provide excellent analgesia over a limited field and with minimal systemic effects. The blocks are generally easy to perform, inexpensive and very safe. Peripheral blocks are possible for nearly all kinds of surgery (Figure 1). Even in situations where the block is ineffective for surgery, the catheter can often be used for postoperative pain management. The technique is under-used both for surgery and for postoperative pain treatment. Peripheral nerve blocks have extended the indications for day-case surgical procedures such as major shoulder surgery and knee reconstruction. Comparative studies of interscalene block and general anaesthesia for day-case shoulder arthroscopic surgery showed that 8% of the patients receiving general anaesthesia required unanticipated admission compared with none in the patients receiving interscalene block.[17 26] Details about different blocks and techniques are beyond the scope of this review; they can be found in standard books.

Upper extremity blocks for day surgery

Several techniques are available to provide efficient regional anaesthesia of the upper limb for day-case surgery. The technique chosen should be appropriate for the intended surgery. The timing of the block is important. It is not advisable to squander operation-room time on waiting for the block to work. Special block rooms outside the operating rooms should be available to (i) handle the high volumes and rapid turnover of patients; (ii) perform the blocks well in advance of the scheduled surgery allowing sufficient 'soak time' (≥20 min) for the local anaesthetic to work; and (iii) recognize early any technical failure so that the decision to proceed with rescue block or general anaesthesia can be made quickly once the patient arrives in the operating room. The block should have residual analgesia in the postoperative period, minimizing the need for systemic analgesics. The limb with residual motor block should be protected appropriately until complete resolution of the block. Criteria for fast-track discharge should be established to minimize patient's recovery and discharge times. In some institutions, patients are allowed to leave before regression or resolution of the block. A telephone follow-up the next day monitors patient satisfaction and any post-surgical complications.[62] During surgery, a tranquil environment should be provided for the patient by allowing them to watch a video, listen to music, or sleep lightly, with judicious use of midazolam if necessary.

Many techniques are available to block the brachial plexus; the most commonly used are interscalene block for shoulder surgery, supraclavicular or interscalene block for upper arm surgery, axillary or intraclavicular block for elbow or forearm surgery and axillary or peripheral nerve block for wrist and hand surgery. The medial, ulnar and radial nerves may be blocked using consistent anatomic landmarks at the elbow or wrist and small volumes of local anaesthetic.

Peripheral nerve blockade can also be used to supplement patchy brachial plexus anaesthesia or provide anaesthesia to a specific site in which surgery is limited and of short duration.

Both bupivacaine and ropivacaine appear to be as efficacious as long-acting local anaesthetics for brachial plexus block.[48] Opioid and non-opioid adjuncts have been added to local anaesthetic solutions in an attempt to improve or prolong analgesia during brachial plexus blockade. Although several studies have reported that analgesia lasts longer when opioids such as morphine, sufentanil and buprenorphine are added to local anaesthetic, other studies found no advantages.[62] Clonidine 0.5 $\mu g\ kg^{-1}$ is reported to prolong anaesthesia and analgesia, but higher doses (e.g. 300 μg) can cause sedation and hypotension, both of which are undesirable in day-surgery patients.[14]

Lower extremity blocks for day surgery

A combined block of the lower extremity offers many advantages over spinal or epidural anaesthesia, such as less hypotension, no urinary retention or post-spinal headache, and fewer concerns regarding bleeding risk in patients taking anticoagulants. For knee surgery, the extent of sensory and motor blockade achieved with a combination of a sciatic and a dorsal lumbar plexus nerve block is comparable to that achieved with a central nerve block. For surgery below the knee, popliteal sciatic nerve block alone or combined with a saphenous nerve block is a reasonable choice; for foot surgery an ankle block is probably the best method. The choice of local anaesthetic depends on duration of the surgery, but attention should be paid to the possibility of systemic toxicity because combined proximal nerve blocks of the lower extremity frequently require doses that are close to the maximum recommended doses. The arguments against peripheral nerve blocks are that they take longer, it is impossible to block all nerves of the lower extremity from one injection site, and there is a certain proportion of failed blocks, even in experienced hands. However, acceptance of peripheral blocks by patient (and surgeon) can be increased by selection of appropriate blocks, patient education and follow-up routines.[31]

Intra-articular analgesia

Intra-articular drug administration has gained popularity because of its simplicity and efficacy in achieving anaesthesia for diagnostic and operative arthroscopy and for providing postoperative analgesia. Although the knee joint has been examined most commonly, arthroscopy of other joints such as shoulder, ankle, wrist, metatarsophalyngeal and temporomandibular joints is being increasingly practised.[27] Intra-articular instillation of local anaesthesia during arthroscopic procedures has been used by many orthopaedic surgeons to provide pain relief after surgery. However, there are conflicting reports in the literature about its therapeutic role. A systematic review of 20 controlled trials with data from about 900 patients showed evidence for a postoperative analgesic effect in 12 of the 20 studies of intra-articular administration of local anaesthetic following arthroscopic knee surgery. However, the evidence was not compelling and, in most cases, analgesia was short lived. Nevertheless, the authors concluded that the technique may be of clinical significance in day-case surgery.[61] The use of intra-articular morphine is effective in the management of pain after arthroscopic knee surgery[86] and anterior cruciate ligament repair.[45] A systematic review of 36 randomised control trials showed that intra-articular morphine may have some effect in reducing postoperative pain intensity and consumption of analgesics.[46] However, most of the studies had significant problems in design, data collection and statistical analysis. The authors emphasized the need for better methodological quality trials to decide conclusively if intra-articular morphine analgesia is clinically useful. There is some evidence that intra-articular NSAIDs have a clinically relevant peripheral analgesic action.[83] Current evidence suggests that intra-articular multimodal regimens may provide improved effects on postoperative pain and convalescence.[10 34 83]

Central neural blockade: epidural, spinal or combined spinal epidural?

Spinal and epidural anaesthesia are effective alternatives to general anaesthesia in ambulatory surgery, with some investigators demonstrating advantages of fewer side-effects and earlier discharge times. However, this remains a controversial issue, as some clinicians are concerned about delayed patient recovery. Selection of short-acting local anaesthetic drugs is therefore appropriate. Combinations of local anaesthetics, short-acting opioids and non-opioids may be used to allow lowest possible effective dose of local anaesthetic to provide early postoperative ambulation and discharge.

The choice of a central block depends on patient request, surgical considerations and anaesthetic benefits. For surgical procedures with patients lying face down, there may be a problem with airway control and general anaesthesia unless endotracheal intubation is used. Anaesthetic benefits with central blocks are most evident in the postoperative phase. The patient may be wheeled out immediately after surgery. Residual block protects the patient from initial pain and there is some evidence that regional anaesthesia also protects the patient from pain after the block has worn off. Patients are in less need of postoperative opioids for pain relief and there is less tendency for nausea or vomiting after central blocks.[32 68] This is a major benefit in day-case surgery, both in terms of better patient comfort and faster discharge. The risk of major neurological complications is very small. However, the patient should be informed about the symptoms of epidural haematoma or abscess formation, because these complications have been reported after discharge of day patients.[67 68]

Epidural anaesthesia with a short-acting local anaesthetic such as lidocaine provides about 60–90 min of anaesthesia with possible discharge 4–6 h after the block. However, it has some drawbacks. It is more time consuming to perform and there is a delay in onset of block. Ræder describes a technique aimed at reducing the time required to achieve an adequate epidural block: the total dose of local anaesthetic is injected as a bolus into the epidural needle, the test dose is eliminated and the surgical site prepared before the block is evident.[68]

Spinal anaesthesia is the most common central block in a day-surgery setting. Spinal block has distinct advantages over epidural anaesthesia, with less time required to achieve an adequate block, lower incidence of incomplete sensory and motor block and pain during surgery.[81]

The spinal technique is easy to perform and has a very high success rate and an enviable safety record.[9] The outpatient spinal anaesthetic is typically of rapid onset, predictable duration, minimal side-effects and reliable offset.[39] Spinal anaesthesia provides excellent surgical conditions for orthopaedic surgery on lower extremities, for gynaecological, urological and perirectal procedures and for lower abdominal procedures such as inguinal hernia. A 17-nation European survey of 105 hospitals showed that almost 40% of all ambulatory surgery in the participating hospitals was performed under regional blocks. Spinal and epidural blocks were used in 25–30% of hospitals. However, there was a great difference between European countries: these blocks were well accepted in Scandinavian countries, Germany and Switzerland, whereas Austria, Greece and Ireland restricted the use of these blocks in day-case surgery.[69] A recent Swedish survey showed that spinal block was used routinely in 85% and epidural block in 28% of the 109 day surgery units in the country (Rawal N, unpublished data).

Lidocaine is used most frequently, though recent studies have shown that transient neurological symptoms (TNS) can occur in 16–40% of outpatients.[35 56 66] Alternative local anaesthetic drugs such as bupivacaine in small doses (5–10 mg) and ropivacaine are associated with a very low incidence of TNS but are not always appropriate for day-case surgery.[39] Adjuvants such as fentanyl 10 µg can improve the success rate of low-dose hyperbaric bupivacaine (e.g. 5 mg) spinal anaesthesia without prolonging discharge time.[13] TNS should be taken into account when considering the choice of local anaesthetic, especially when the lithotomy position or knee arthroscopy is planned.[39] In a recent study, mepivacaine 60–80 mg was shown to be a suitable anaesthetic choice for ambulatory spinal anaesthesia with respect to anaesthetic, as well as recovery profiles. A postoperative follow-up did not show TNS in any of the 60 patients who received spinal mepivacaine as part of combined spinal–epidural (CSE) for anterior cruciate ligament repair.[64]

A former barrier to outpatient spinal administration, namely post-dural puncture headache, has been largely eliminated with the introduction of conical-tipped needles that result in less dural trauma. Comparative studies of spinal and general anaesthesia have dispelled the myth that spinal anaesthesia results in operating room inefficiency. Novel manipulations of baricity and dose have resulted in significant reductions in unwanted motor block using conventional spinal anaesthesia.[39 66]

For surgical procedures involving one lower limb, a unilateral spinal block has been shown to minimize the haemodynamic effects of spinal anaesthesia. The technique involves the lateral decubitus position, low-dose hyperbaric local anaesthetic solution, low speed of intrathecal injection and directional pencil-point spinal needles.[19] Unilateral spinal block for ambulatory surgery needs further evaluation.

Selective spinal anaesthesia (SSA) using lower doses of intrathecal agents with or without intrathecal or systemic adjuvants has been used to provide spinal anaesthesia with greater selectivity and rapid return of function. It has been demonstrated that SSA provides pinprick analgesia suitable for surgery while light touch, proprioception, motor and sympathetic function are preserved.[91]

CSE anaesthesia combines the rapidity, density and reliability of subarachnoid block with the flexibility of continuous epidural block.[77] Although, at first sight, CSE techniques appear to be more complicated than epidural or spinal block alone, intrathecal drug administration and siting of the epidural catheter are both enhanced by the combined, single-space, needle-through-needle method. CSE is an effective way to reduce the total drug dosage required for anaesthesia and analgesia, thus making a truly selective blockade possible.[77] In contrast with epidural anaesthesia, the other leading central neuraxial technique, CSE, has a lower failure rate and a faster onset time.[40] The practicality of CSE has been questioned. CSE is well-established for inpatient surgery and obstetrics but is still in its infancy in day-case surgery. By providing the 'safety net' of an epidural catheter, CSE allows use of the lowest effective dose of local anaesthetic.[65 90] For ambulatory knee surgery, CSE allowed Urmey and colleagues to reduce the dose of spinal lidocaine from 80 mg to 40 mg.[90] Similarly, Pawlowski and others used CSE to identify appropriate doses of spinal mepivacaine in order to eliminate the risk of TNS.[64] The security of an epidural catheter allows minimal dosing of local anaesthetic and therefore more precise predictability of day surgery spinal anaesthesia.

Strategies for postoperative pain management

Optimal postoperative pain control for day-case surgery should be effective and safe, produce minimal side-effects, facilitate recovery and be easily managed by patients at home. Analgesic techniques should permit 'normal' activities and additional analgesic supplements should be provided to cover any painful activity. Rescue analgesia should be provided if the prescribed analgesic is ineffective. The use of pre-packaged take-home analgesics specific to the type of surgery and breakthrough medication can lead to improved pain control, mobility and sleep.[58]

Pain assessment and documentation

Pain intensity must be assessed and reassessed frequently and documented on the bedside chart ('making pain visible'). The day-care facility should define a maximum acceptable pain score and train the personnel to treat pain promptly if it exceeds a certain level. At our institution, a hospital-wide policy of keeping pain levels at ≤3 on the 10-point visual analogue scale (VAS) has been functioning satisfactorily since 1991 for surgical day-case and inpatients. Pain intensity is assessed and documented every 3 h for inpatients and at least every hour for day-case surgery patients.[71] It is important to assess pain and efficacy of analgesia at rest and during activity. A practical scheme is to assess pain at rest in early recovery, and at rest *and* during activity at and after discharge. In situations where communication is difficult, a verbal or observer (nurse) scoring system can be used[82] (Figure 2). It may be difficult to determine whether small children are in pain after surgery because such children are unable to express their feelings in words. If a child's pain is treated at home, parents have to estimate the level of pain and therefore need to be informed appropriately. Pain assessment tools have been formulated and validated for parents to use at home.[20 95] Documentation of pain scores also allows the day surgery unit (DSU) to perform regular audits to confirm that pain management techniques are not causing problems at home.

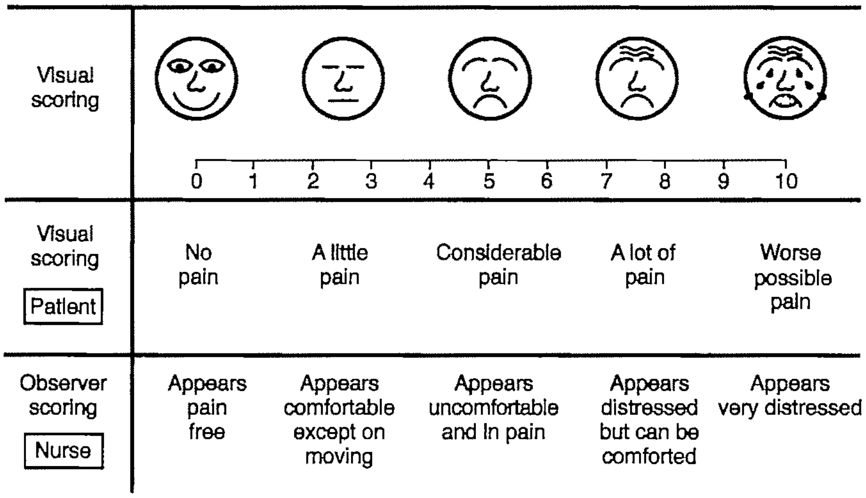

Fig 2 Pain scoring systems (modified from reference 82).

Pain management in the PACU

postoperative pain control should be started intra-operatively by supplementing general anaesthesia with short-acting opioids, NSAIDs or regional anaesthesia. This should aid smooth recovery. When opioids are used in the recovery period, rapid and short-acting drugs such as fentanyl and alfentanil should be administered i.v. and titrated to desired effect.

Regional analgesia performed in conjunction with general anaesthesia is becoming an increasingly important component of paediatric postoperative pain management. A variety of regional blocks can be performed simply and quickly in paediatric day-surgery patients.

The possible differences in PONV between different opioids have not been demonstrated in controlled trials: no difference in adverse effects was noted between morphine, pethidine (meperidine) and fentanyl (in adults) using PCA[97] or between i.v. morphine and i.v. fentanyl in the PACU.[23] Incidence of nausea and vomiting increases significantly in the period after discharge, because morphine can act as an emetic stimulus on the trip home, resulting in delayed vomiting. Discharge may also be delayed by PONV and sedation. Combinations of analgesics that act by different mechanisms result in additive or synergistic analgesia, allowing total doses of drugs to be reduced and so reducing side-effects. Such techniques, using a combination of opioid, NSAID, paracetamol and local anaesthetic, are superior to any single modality. Regular and frequent assessment of pain intensity is important. Differences between analgesic methods may only become evident when pain is assessed during activity, so pain should be assessed both at rest and during activity.[82]

Choice of analgesic after discharge

Oral analgesics are the mainstay of continuing pain control at home, and it is important to encourage patients to take analgesics pre-emptively and regularly, starting before the effect of the local anaesthetic has worn off.[81] For mild pain, simple analgesics such as paracetamol may be sufficient. Patients with mild to moderate pain in day surgery benefit from combinations of NSAIDs and weak opioids in addition to regional or local anaesthesia. Patients' responses to drugs vary, so rescue analgesia for postoperative pain beyond acceptable levels may be needed. Strong opioids are generally avoided because of their well-known side-effects, including the risk of respiratory depression.

Paracetamol is the most commonly used analgesic worldwide because it is effective, cheap and safe. It is often combined with other drugs, such as weak opioids and NSAIDs, as part of a balanced analgesic approach. The effectiveness of paracetamol is often underestimated because this drug is often not administered correctly. Paracetamol has a dose-related potency for postoperative pain in paediatric surgery.[51] Earlier dosing with paracetamol 10–15 mg kg^{-1} 'as necessary' failed to provide therapeutic plasma concentrations and so was ineffective.[96] In children, a loading dose of 40 mg kg^{-1} (or greater) is currently recommended followed by regular dosing of 90 mg kg^{-1} day^{-1} to maintain therapeutic plasma concentrations.[3 96 98]

The currently recommended doses for rectal and oral administration of paracetamol are the same. However, the rectal dose should be higher than the oral dose, because of poor and erratic absorption of paracetamol from suppositories.[3 51]

Weak opioids, such as codeine and dextropropoxyphene, are the most commonly used oral opioids, usually in combination with paracetamol. Tramadol is believed to have a potency equal to that of pethidine[28] without causing significant respiratory depression. Its main drawback is a high incidence of nausea and vomiting. Our recent controlled comparison between tramadol, metamizol and paracetamol in patients undergoing day-case hand surgery showed that none of the study drugs provided effective analgesia in all patients. The percentage of patients who required rescue dextropropoxyphene at home was 42% with paracetamol, 31% with metamizol and 23% with tramadol. However, tramadol was associated with the greatest frequency and severity of adverse effects such as nausea and dizziness and, consequently, with the greatest dissatisfaction. Metamizol and paracetamol provided good analgesia in 70% and 60% of the patients, respectively, with low incidence of side-effects.[78]

NSAIDs are now the basis of most day-surgery analgesic regimes. As well as providing effective analgesia, their anti-inflammatory effects may help reduce local oedema and minimize the use of more potent drugs and their accompanying side-effects. Several advantages are offered by NSAIDs in the peri-operative period. They are effective as the sole analgesic in a high proportion of cases of mild to moderate pain. When combined with opioids, they can enhance the quality of opioid-based analgesia and often diminish opioid requirements by about 25%. Some studies have shown that they may reduce opioid-related side effects.

NSAIDs are frequently used to treat mild to moderate pain and as a component of multimodal regimens for moderate to severe pain. In 1998, the Royal College of Anaesthetists issued guidelines for the use of NSAIDs in the peri-operative period. Based on the strongest evidence available, it is stated that 'In situations where there are no contraindications, NSAIDs are the drug of choice after many day-case procedures.'[80] However, controversy still surrounds the use of NSAIDs because of their significant gastrointestinal, haematological and renal side effects. Systematic reviews have not found any important differences between different NSAIDs but have found differences in toxicity related to increased doses and possibly to the NSAID itself. It has been proposed that the anti-inflammatory properties of NSAIDs are mediated through cycloxygenase 2 (COX-2) inhibition, whereas adverse effects occur as a result of their effects on COX-1. The World Health Organization has categorized COX-2-selective drugs as a new subclass of NSAIDs (coxibs). The two coxibs currently available, rofecoxib and celecoxib, appear to be as effective as non-selective NSAIDs in suppressing inflammation and providing analgesia, while reducing the incidence of endoscopy-verified ulcers to levels similar to those seen with placebo.[55] Parecoxib is a new COX-2-specific agent that is given i.v. or i.m. The role of COX-2-specific NSAIDs in postoperative pain management will become clearer when the results of ongoing clinical trials become available. Overall, the benefits of NSAIDs greatly outweigh their risks. Choice of drug will depend on availability, desired route of administration (oral, rectal, i.v.), duration of analgesia and cost.

In general, there is a great need for powerful non-opioid analgesics in future day surgery and they may either be prescribed alone or be used to reduce opioid requirements. It may prove more convenient and less unpleasant to give these drugs by the i.v. route rather than by i.m. or rectal administration.

Regional techniques at home

Administration of local anaesthetic into the surgical wound is effective and safe but the analgesia lasts only a few hours. We have described a technique using an elastometric balloon pump, which allows the patient to self-administer local anaesthetic analgesia at home.[75] The technique involves placement of a multihole, thin (22-gauge) epidural or Perifix brachial plexus catheter (B. Braun, Melsungen, Germany) subcutaneously into the surgical wound, subacromially, intra-articularly or in the axillary brachial plexus sheath (depending on the surgical site). The catheter is tunnelled 4–5 cm subcutaneously by the surgeon and firmly secured on to the skin by sterile tape. Axillary brachial plexus catheters are placed and secured in position by anaesthetists. The catheters are introduced 3–5 cm within the sheath and secured to the skin with transparent dressing and tape.

Using aseptic technique, the catheters are connected to a 50 or 100 ml elastomeric (balloon) pump (Figure 3) with the appropriate concentration and volume of local anaesthetic drug ('Home Pump'; I-Flow Corporation Lake Forest, CA, USA). The balloon pump is filled with a volume of local anaesthetic to provide 10 doses for postoperative pain management. After the operation, when the patient feels pain, he starts the local anaesthetic infusion by opening the clamp. The patient stops the infusion by closing the clamp after the prescribed time (usually 6 min), or earlier if he is satisfied with pain relief (Figure 3). When the patient no longer requires analgesia, he removes the tape, pulls out the catheter and discards the pump. In most cases, the patient gives himself the first dose in the PACU.

In brachial plexus catheters, 0.125% bupivacaine or ropivacaine was used, whereas 0.25% was used in all other catheters. The 0.125% solution was used to reduce or avoid the risk of possible injury caused by excessive motor block. The maximum volume of local anaesthetic allowed for each administration was 2.5 ml for maxillofacial surgery, 5–10 ml for surgical wounds and 10 ml for other procedures. An appropriately sized pump (50 or 100 ml) filled with local anaesthetic to provide 10 doses at home was given to the patient before discharge. The patient was told not to use the pump more than once an hour. Follow-up consisted of evaluation of pain relief at home, pump function, use of rescue medication and overall satisfaction or dissatisfaction with the technique.

Pain relief was graded as good to excellent by 90% of patients. Onset of analgesia was experienced within 5 min, and the duration of analgesia after each administration of local anaesthetic varied from 2 to 8 h. Patient follow-up did not reveal any infection or any other major problem with the technique, and patient satisfaction was very high. Nearly

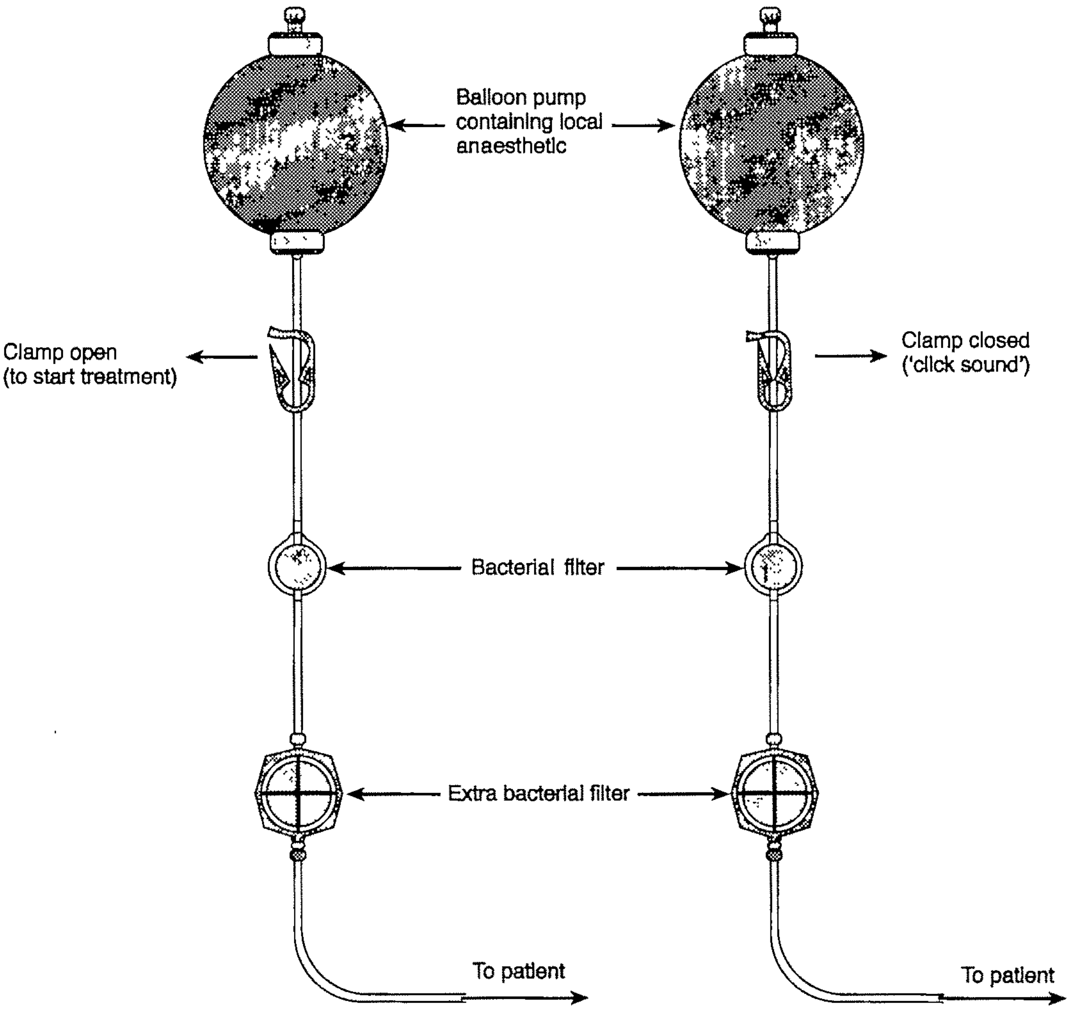
Balloon pump containing local anaesthetic
Clamp open (to start treatment)
Clamp closed ('click sound')
Bacterial filter
Extra bacterial filter
To patient
To patient

Fig 3 Self-administration of local anaesthetic solution by a patient. On opening the clamp (left), the solution starts running into the catheter. After the prescribed time (usually 6 min), the patient closes the clamp (confirmed by a clicking sound) to stop the infusion (right). The patient is encouraged to use a timer as a reminder to close the clamp. (Reprinted from reference 73 with permission from Lippincott–Williams and Wilkins.)

700 patients undergoing a variety of surgical procedures have been treated with patient-controlled regional anaesthesia (PCRA) at our hospital without any major complications.

Recent controlled trials have demonstrated the efficacy and safety of incisional catheter PCRA in patients undergoing Caesarean section,[100] abdominal hysterectomy[99] and inguinal hernia repair.[92] Our controlled comparison between 0.125% ropivacaine and 0.125% bupivacaine for axillary brachial plexus PCRA at home demonstrated the feasibility, efficacy and safety of this technique for treating pain outside the hospital. Both drugs provided effective analgesia, but patient satisfaction was better with ropivacaine PCRA.[76] White cell counts, bacterial culture of the catheter tips and wound inspection have not shown any evidence of infection.[92 99]

The main concern with the balloon pump device is the risk of local anaesthetic toxicity if the patient neglects to close the clamp. This can be prevented with newer devices which allow a continuous infusion of local anaesthetic at a pre-set rate. For example a 100 ml elastomeric pump ('Pain Buster'; I-Flow Corporation, Lake Forest, CA, USA) can provide adequate analgesia at home for 2 days when the local anaesthetic is infused at a rate of 2 m h^{-1}. However, this is not PCRA. Newer, lightweight pumps with appropriate safety features including lock-out possibilities and disposable cassettes for local anaesthetic solutions are also available to provide safe PCRA in the patients' home environment (Microject; Sorensen Medical, UT, USA). Further studies are necessary to establish the efficacy and safety of this promising new technique at home after ambulatory surgery. Studies are also necessary to evaluate the optimal concentration and volume of local anaesthetic and the possible role of adjuvant drugs. Adequate patient information is important (Table 3).

Role of patient (and parent) information

Preoperative preparation of patients

Postoperative pain is often associated with anxiety; it has been demonstrated that patient education and preoperative

Table 3 Patient instructions for post-operative PCRA at home

The patient should be given oral and written information about the technique and how the 'balloon pump' works. Information should also include the following:

- importance of opening and closing the clamp at prescribed times (use of a timer is encouraged)
- details of how to remove catheter at the end of treatment
- importance of good hygiene near the wound area
- name and telephone (and pager) number(s) of physician to be contacted in case of local anaesthetic toxicity symptoms or other problems
- request for the patient to return follow-up data (about technique and satisfaction) in self-addressed envelope

Telephone follow-up day after surgery by a nurse or physician

Table 4 Day-case surgery: infomation given before discharge

- Explain that 20–40% patients may have moderate to severe pain at home and that it can last 2–4 days.
- Advise patients on how to manage pain (which drug(s)? how often?) and side-effects of analgesic drugs.
- Provide (or prescribe) breakthrough analgesic (and antiemetic) in addition to regular medication to last 2–4 days.
- Advise patients to take analgesic before the effect of single dose local anaesthetic wears off.
- Encourage parents to use a pain assessment tool to optimize paediatric pain control.
- Explain that post-operative tiredness and drowsiness are common and in some patients may last several days.
- Provide telephone number and pager number of physician to be contacted if necessary.
- Inform the patient that a follow-up call will be made by the surgeon or nurse on the day after surgery.

preparation can reduce postoperative pain.[36] Successful postoperative pain control depends on the knowledge and demands of the patient. A questionnaire survey for evaluating the general public's perception of postoperative pain revealed that almost half of patients were prepared to suffer pain rather than complain.[84] Patients should be informed about the need to treat pain and about the various ways of managing pain. The information should be given verbally and in writing. Day patients with severe pain at home do not always take their medication as prescribed and may even mix in their own analgesics. Clear instructions are therefore mandatory. On admission to DSU, pain management should be discussed with the patient and the pain assessment scoring explained. Patient preferences, for example with regard to the use of suppositories or central neuraxial blocks, should be respected.

Analgesia needs to be tailored to the severity of pain associated with the procedure. Drugs are chosen on the basis of their availability, freedom from side-effects, convenience of administration and safety. Patients' responses to drugs vary, so rescue analgesia for pain beyond acceptable levels may be needed. Pre-packaged analgesics should be provided for anticipated mild, moderate or severe pain. A follow-up call the next day reassures the patient and provides feedback about analgesic efficacy. Regular audit of the postoperative pain service is essential.[82]

For patients undergoing surgery with regional anaesthetic techniques, patient education during the pre-operative clinic visit is essential to improve patient acceptance of the use of regional anaesthesia. Audiovisual material and an information pamphlet are helpful tools, giving patients time to make an intelligent decision and to be psychologically prepared for the block. Patient education will also help to allay apprehension about being awake during the surgery and to address the fear of pain during block.

Local anaesthetics such as bupivacaine should be chosen for their long-lasting effect. All surgeons should be encouraged to use bupivacaine for wound infiltration. However, patients should be warned that the effects will wear off and that they should take another analgesic before this happens, particularly before going to bed on the first night after surgery. Patients must meet standard discharge criteria following day surgery with local or regional anaesthesia. Patients who have undergone central neural blockade should have return of motor and sensory function and preferably void before discharge. Those who have residual numbness after limb anaesthesia should be advised about limb protection[17] (Table 4).

Prevention and treatment of pain and PONV at home remain a challenge in children undergoing day-case surgery. The parents of a child recovering at home have to estimate the intensity of pain and treat postoperative pain. A general instruction to parents to give the child some medication for pain at home as needed is not enough. To ensure successful pain management at home, it is important to give parents appropriate information. It is also important to train doctors and nurses to provide proper information on treating pain and to determine the outcomes of training programmes. Since hospital personnel often recommend over-the-counter pain medicines, we should also direct attention to pharmacists' knowledge of pain treatment in children and their ability to provide information for parents. Staff training programmes to provide adequate information about postoperative pain medication for the parents can be highly beneficial.[85]

Future perspectives in day-case surgery and pain management

Advances in day-case anaesthesia and development of minimally invasive surgical techniques can be expected to continue. Day-case surgery has presented a new set of challenges and goals for the anaesthetist. Newer inhalational agents and improved anaesthetic drugs with minimal emetic sequelae and new drug delivery techniques may improve the outcome of day-case surgery in the future. Widespread use of improved sedation and regional anaesthesia will also evolve. Further development of target infusion anaesthesia will smooth the maintenance of day-case anaesthesia.[15] Although the requirement for alternative analgesia immediately after cessation of infusion limits the usefulness of remifentanil in day-case surgery, further advances in opioid therapy may become available with the introduction of trefentanil and mirfentanil. The former has characteristics intermediate between those of alfentanil and remifentanil.[16 63] Patient-controlled approaches to newer opioid drug delivery systems, such as transdermal iontopheresis[7] or intranasal[87] or transmucosal[6] delivery also need to be evaluated for their suitability and safety in patients discharged after day-case surgery. Based on current trends, it is fair to predict an increased use of local or regional anaesthesia alone, in combination with sedation anaesthesia or as part of a multimodal technique with general anaesthesia. As more extensive and painful procedures, such as cholecystectomy, knee reconstructions, shoulder procedures, hysterectomy and laminectomy, are being performed as day surgery, there will be a pressing need to introduce far better drugs to alleviate PONV and pain.

Spinal and epidural blockade are widely practised in several countries. Discharge times of 2–3 h after short-acting local anaesthetics or low-dose local anaesthetic drug combinations are not unrealistic.[30] Patient acceptance will increase if the benefits of these procedures are explained by enthusiastic surgeons and anaesthetists. It is no longer valid to oppose spinal anaesthesia on account of post-lumbar puncture headache. This may be reduced to less than 1% by the use of 26- or 27-gauge pencil-point spinal needles.[39] Further improvements in needle and catheter technology will make central neuraxial blocks safer. The trend towards increasing use of peripheral nerve blocks[42] will accelerate as newer catheter systems (e.g. Stim-Kath, Epimed) become available which allow successful placement by nerve stimulation technique.[1] The recent introduction of less toxic long-acting local anaesthetics ropivacaine and levobupivacaine have improved the safety of regional techniques. A variety of opioid and non-opioid adjuvants to local anaesthetic drugs are under investigation. Other future directions in the use of regional anaesthesia for day-case surgery include the development of local anaesthetic encapsulated in lipophilic membranes, which allows sustained release of local anaesthetic and thus prolonged analgesia lasting several days after single injection techniques.

Although the concept of fast-tracking is well accepted in day-case surgery, the issue of at-home recovery is generally neglected. Almost all literature concerns the early postoperative period while the patient is in hospital. At-home recovery and return to normal daily activities are of greater interest to the patient, his family and society. The following questions need to be addressed. What is the natural course of recovery after different surgical procedures? When is cognitive function restored to baseline? When do patients resume usual at-home activities? What is the relationship between hospital costs and costs to society?

Conclusions

Day surgery is a cost-effective, quality approach to surgery that has expanded rapidly in recent years. Multiple factors have contributed to this transition, including economic forces, improved anaesthetic and surgical techniques, better pre-operative planning, better patient education and an enhanced ability to deliver adequate analgesia in the outpatient setting. Many procedures that used to be performed on an in-patient basis under general anaesthesia are now performed on a day basis under local or regional anaesthesia alone or combined with sedation techniques.

Regional anaesthesia offers many advantages for the day-case surgery patient. Patients can remain alert and, with proper techniques and agents, are able to be rapidly discharged with minimal side-effects and optimal pain control. Local and regional anaesthesia, alone or as part of general anaesthetic technique, offer major benefits to the ambulatory surgery patient. In general, peripheral nerve blocks are under-used for ambulatory surgery. The use of regional techniques will depend on local tradition, the day-surgery facility, patient and surgeon co-operation and skill of the anaesthetists. In many institutions, neuraxial blocks such as epidural, spinal, and CSE are controversial regional techniques for day-case surgery. However, by appropriate patient selection, choice of equipment, drugs and adjuvants, the anaesthetist can tailor neuraxial blocks to a specific type and duration of surgery.

The success of day-case surgery depends, to a large extent, on both effective control of postoperative pain and minimization of side-effects such as sedation, nausea and vomiting. Inadequate analgesia after surgery is a problem: it has been demonstrated that one-third of patients suffer moderate to severe postoperative pain as a result of inadequate analgesia. Under-treatment is still one of the most common errors in the treatment of pain in children. Day-surgery analgesia must allow the patient to be discharged safely and without delay. Additionally, after the patient has been discharged, he must not require close medical or nursing supervision, either for the administration of analgesia or for safety reasons. Side-effects that might be regarded as minor in the inpatient may contribute to unexpected admissions in the day-case setting. Prolonged recovery may disrupt patient flow and increase institutional costs per patient. The unplanned overnight hospital admission rate may well reflect the quality of care in day-case surgery.

The growth of day-case surgery requires both a rapid return to street fitness and the provision of analgesia appropriate to the nature of the surgery undertaken. Balanced analgesia in day-case surgery commonly involves intra-operative administration of short-acting opioids such as fentanyl, and wound infiltration with local anaesthetic at the end of surgery supplemented in the postoperative period by an oral, non-opioid analgesic. Recent improvements in our pharmacological knowledge concerning pain medication have made it possible to provide more individualized pain treatment for adults and children.

Dispensing appropriate analgesia with clear instructions for the patient is crucial. Giving patients pre-packed analgesics for anticipated mild, moderate or severe pain, with clear directions has the potential for improving patient comfort at home. After discharge, patient follow-up is essential to monitor effectiveness of pain treatment. Day-surgery units should standardize and audit their analgesic treatments for mild, moderate and severe pain. New portable PCRA systems are becoming available which can provide effective and safe analgesia at home for several days. Small disposable pumps, pre-loaded with local anaesthetic, with pre-set hourly infusion rates or self-administered bolus infusions provide effective analgesia at home.

References

1 Aither MH, Goroszenuik T, Sanderson K. Trial peripheral nerve stimulation via stimulating epidural catheter for neuropathic pain. *Int Monitor Reg Anaesth* 2000; **12**: 42

2 Andersen R, Krogh K. Pain as a major cause of postoperative recovery with conventional technique. *Br J Anaesth* 1996; **77**: 576–80

3 Anderson BJ. What we don't know about paracetamol in children. *Paediatr Anaesth* 1998; **8**: 451–60

4 Anderson BJ, Woolard GA, Holford NHG. Pharmacokinetics of rectal paracetamol after major surgery in children. *Paediatr Anaesth* 1995; **5**: 237–42

5 Apfelbaum JL, Grasela TH, Walawander CA, SAFE study team. Bypassing in PACU: a new paradigm in ambulatory surgery. *Anesthesiology* 1977; **87**: A32

6 Ashburn MA, Lind GH, Gillie MH *et al.* Oral transmucosal fentanyl citrate (OTFC) for the treatment of postoperative pain. *Anesth Analg* 1993; **76**: 377–81

7 Ashburn MA, Streisand J, Zhang J *et al.* The iontophoresis of fentanyl citrate in humans. *Anesthesiology* 1995; **82**: 1146–53

8 Atanassoff PG, Hartmannsgruber MWB. Is ropivacaine 0.2% an alternative to lidocaine 0.5% for intravenous regional anesthesia? *Br J Anaesth* 1998; **80**: A377

9 Auroy Y, Narchi P, Messiah A. Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology* 1997; **87**: 479–86

10 Axelsson K, Johanzon E, Gupta A, Ekbäck G, Rawal N, Nordenson U, Berg E. Intra-articular administration of ketolorac, morphine and ropivacaine for pain relief after shoulder surgery. *Int Monitor Reg Anesth* 2000; **12**: 81

11 Barst SM, Markowitz A, Yossefy Y, Abramson A, Lebowitz P, Bienkowski RS. Propofol reduces the incidence of vomiting after tonsillectomy in children. *Paediatr Anaesth* 1995; **5**: 249–52

12 Beauregaard L, Pomp A, Choinière M. Severity and impact of pain after day-surgery. *Can J Anaesth* 1998; **45**: 304–11

13 Ben-David B, Solomon E, Levin H. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. *Anesth Analg* 1997; **85**: 560–5

14 Bernard JM, Macaire P. Dose range effects of clonidine added to lidocaine for brachial plexus block. *Anesthesiology* 1997; **87**: 277–84

15 Bovill JG. New delivery systems for anaesthesia. *Curr Opin Anaesthiol* 1995; **8**: 287–91

16 Bovill JG. New drugs. *Curr Opin Anaesthiol* 1996; **9**: 318–22

17 Brown AR, Weiss R, Greenberg C *et al.* Interscalene block for shoulder arthroscopy: comparison with general anesthesia. *Arthroscopy* 1993; **9**: 295–300

18 Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg* 1999; **86**: 1528–31

19 Casati A, Fanelli G, Capelleri G *et al.* Low dose hyperbaric bupivacaine for unilateral spinal anaesthesia. *Can J Anaesth* 1998; **45**: 850–4

20 Chambers CT, Reid GJ, McGrath PJ *et al.* Development and preliminary validation of a postoperative pain measure for parents. *Pain* 1996; **68**: 307–13

21 Chan VWS, Weisbrod MJ, Kaszas S *et al.* Comparison of ropivacaine and lidocaine for intravenous regional anesthesia in volunteers. A preliminary study on anesthetic and blood levels. *Anesthesiology* 1999; **90**: 1602–8

22 Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. *Anesth Analg* 1997; **85**: 808–16

23 Claxton AR, McGuire G, Chung F, Cruise C. Evaluation of morphine versus fentanil for postoperative analgesia after ambulatory surgical procedures. *Anesth Analg* 1997; **84**: 509–14

24 Cushiere A. Day case (ambulatory) laparoscopic surgery. Let us sing from the same hymn sheet. *Surg Endosc* 1997; **11**: 1143–4

25 Dahl V, Gierløff C, Omland E, Ræder J. Spinal, epidural or propofol anaesthesia for outpatient knee arthroscopy? *Acta Anaesthesiol Scand* 1997; **41**: 1341–5

26 D'Allessio JG, Rosenblum M, Shea KP *et al.* A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. *Reg Anesth* 1995; **20**: 62–8

27 De Andrés J, Monzo E. Regional techniques for day surgery: intra-articular anesthesia and analgesia. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 54–61

28 Eggers KA, Power I. Tramadol. *Br J Anaesth* 1995; **74**: 247–9

29 Finley GA, McGrath PJ, Forward SP, McNeill G, Fitzgerald P. Parents' management of children's pain following 'minor' surgery. *Pain* 1996; **64**: 83–7

30 Fortier J, Chung F, Su J. Predictive factors of unanticipated admission in ambulatory surgery: a prospective study. *Anesthesiology* 1996; **85**: A27

31 Gligorijevic S. Lower extremity blocks for day surgery. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 30–7

32 Greenberg CP. Practical, cost-effective regional anesthesia for ambulatory surgery. *J Clin Anesth* 1995; **7**: 614–21

33 Guignard B, Bossard AE, Coste C *et al.* Acute opioid tolerance. Intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; **93**: 409–17

34 Gupta A, Axelsson K, Allvin R *et al.* Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. *Reg Anesth Pain Med* 1999; **24**: 225–30

35 Hampl KF, Heinzmann-Wiedmer S, Luginbuehl I. Transient neurologic symptoms after spinal anesthesia: a lower incidence with prilocaine and bupivacaine than with lidocaine. *Anesthesiology* 1998; **88**: 629–33

36 Hekmat N, Burke M, Howell S. Preventive pain management in the postoperative hand surgery patient. *Orthopaed Nursing* 1994; **13**: 3

37 Henderson CL, Warriner CB, McEwen A *et al.* A North American survey of intravenous regional anesthesia. *Anesth Analg* 1997; **85**: 858–63

38 Hitchock M. Postoperative morbidity following day surgery. In: *Practical Anaesthesia and Analgesia for Day Surgery.* Oxford: BIOS Scientific Publishers, 1997; 207–10

39 Hodgson PS, Liu SS. Spinal anesthesia for day surgery. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 3–9

40 Holmström B, Laugaland K, Rawal N *et al.* Combined spinal–epidural block versus spinal and epidural block for orthopaedic surgery. *Can J Anaesth* 1993; **40**: 601–6

41 Holte K, Werner M, Lacouture PG, Kehlet H. Dexamethasone

prolongs analgesia of subcutaneous bupivacaine microspheres in human volunteers. *Int Monitor Reg Anesth* 2000; **12**: 258

42 Horlocker TT. Peripheral nerve blocks—regional anesthesia for the new millenium. *Reg Anesth Pain Med* 1998; **23**: 237–40

43 Jin FL, Chung F. Postoperative pain—a challenge for anaesthetists in ambulatory surgery. *Can J Anaesth* 1998; **45**: 293–6

44 Jolliffe DM. An audit of paediatric day care surgery in a District General Hospital. *Paediatr Anaesth* 1997; **7**: 317–23

45 Joshi GP, McCaroll SM, Brady OH *et al.* Intraarticular morphine for pain relief after anterior cruciate ligament repair. *Br J Anaesth* 1993; **70**: 87–8

46 Kalso E, Tramér MR, Carroll D, McQuay HJ, Moore AR. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain* 1997; **71**: 127–34

47 Katz J. Pain begets pain. Predictors of long term phantom limb pain and post-thoracotomy pain. *Pain Forum* 1997; **6**: 140–4

48 Klein SM, Greengrass RA, Steele SM *et al.* A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block. *Anesth Analg* 1998; **87**: 1316–19

49 Koivusalo A-M, Kellokumpui I, Lindgren L. Gasless laparoscopic cholecystectomy: comparison of postoperative recovery with conventional technique. *Br J Anaesth* 1996; **77**: 576–80

50 Kokki A, Ahonen R. *Pain* and activity disturbance after paediatric day case adenoidectomy. *Paediatr Anaesth* 1997; **7**: 227–31

51 Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetoaminophen in pediatric day-case surgery. *Anesthesiology* 1999; **91**: 442–7

52 Kotiniemi LH, Ryhänen PT, Moilanen IK. Behavioral changes in children following day-case surgery: a 4-week follow-up of 551 children. *Anaesthesia* 1997; **52**: 970–6

53 Kotiniemi LH, Ryhänen PT, Valanne J, Jokela R, Mustonen A, Poukkula E. Postoperative symptoms at home following day-case surgery in children: a multicentre survey of 551 children. *Anaesthesia* 1998; **52**: 563–9

54 Leach A. Old ideas, new applications. *Br J Anaesth* 1998; **81**: 113–14

55 Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs. New and improved? *J Am Med Assoc* 2000; **284**: 1297–9

56 Liguori GA, Zayas VM, Chisholm MF. Transient neurologic symptoms after spinal anesthesia with mepivacaine and lidocaine. *Anesthesiology* 1998; **88**: 619–23

57 Londergan TA, Hochman HI, Goldberg N. Postoperative pain following outpatient pediatric urologic surgery: a comparison of anesthetic techniques. *Urology* 1994; **44**: 572–6

58 Marquardt HM, Razis PA. Prepacked take-home analgesia for day case surgery. *Br J Nursing* 1996; **5**: 1114–8

59 Maunuksela E-L, Ryhänen P, Janhunen L. Efficacy of rectal ibuprofen in controlling postoperative pain in children. *Can J Anaesth* 1992; **39**: 226–30

60 Mikat-Stevens M, Sukhani R, Pappas AL, Fluder E, Kleinman B, Stevens RA. Is succinylcholine after pretreatment with d-tubocurarine and lidocaine contraindicated for outpatient anesthesia? *Anesth Analg* 2000; **91**: 312–6

61 Møiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A systemic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. *Reg Anesth Pain Med* 1999; **24**: 430–7

62 Murphy DB, Chan VWS. Upper extremity blocks for day surgery. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 19–29

63 Ogg TW. The future of day surgery and anaesthesia. In: *Practical Anaesthesia and Analgesia for Day Surgery*. Oxford: BIOS Scientific Publishers, 1997; 237–44

64 Pawlowski J, Sukhani R, Pappas AL *et al.* The anesthetic and recovery profile of two doses (60 and 80 mg) of plain mepivacaine for ambulatory spinal anesthesia. *Anesth Analg* 2000; **91**: 580–4

65 Peng PW, Chan VW, Perlas A. Minimum effective anesthetic concentration of hyperbaric lidocaine for spinal anaesthesia. *Can J Anaesth* 1998; **45**: 122–9

66 Pollock JE, Liu SS, Neal JM. Dilution of spinal lidocaine does not alter the incidence of transient neurologic symptoms. *Anesthesiology* 1999; **90**: 445–50

67 Porterfield WR, Wu CL. Epidural hematoma in an ambulatory surgical patient. *J Clin Anesth* 1997; **9**: 74–7

68 Ræder J. Epidural blocks for day surgery. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 10–2

69 Rawal N. Regional anaesthesia for ambulatory surgery. A European survey. *Br J Anaesth* 1995; **75**: 6

70 Rawal N. European approaches to postoperative pain management. *Tech Reg Anesth Pain Mgmt* 1997; **1**: 93–100

71 Rawal N. 10 years of acute pain services—achievements and challenges. *Reg Anesth Pain Med* 1999; **24**: 68–73

72 Rawal N. Intravenous regional anesthesia. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 51–3

73 Rawal N. Patient-controlled regional anesthesia at home. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 62–6

74 Rawal N, Hylander J, Nydahl P-A, Olofsson I, Gupta A. Survey of postoperative analgesia following ambulatory surgery. *Acta Anaesthesiol Scand* 1997; **41**: 1017–22

75 Rawal N, Axelsson K, Hylander J, Allvin R, Amilon A, Lidegran G, Hallén J. Postoperative patient-controlled local anesthetic administration at home. *Anesth Analg* 1998; **86**: 86–9

76 Rawal N, Allvin R, Hallén J *et al.* Ropivacaine versus bupivacaine for axillary plexus analgesia at home—a controlled trial of PCRA. *Int Monitor Reg Anaesth* 2000; **12**: 199

77 Rawal N, Holmström B, Crowhurst JA, Van Zundert A. The combined spinal–epidural technique. *Anaesthesiol Clin N Am* 2000; **18**: 267–95

78 Rawal N, Allvin R, Amilon A, Ohlsson T, Hallén J. Postoperative analgesia at home after ambulatory hand surgery a controlled comparison between tramadol, metamizol and paracetamol. *Anesth Analg* 2001; **92**: 347–51

79 Roberts BL, Peterson GM, Friesen WT, Beckett WG. An investigation of pain experience and management following gynecological surgery: differences between open and closed surgery. *J Pain Symptom Manage* 1995; **10**: 370–7

80 Royal College of Anaesthesists. *Guidelines for the Use of Non-steroidal Anti-inflammatory Drugs in the Perioperative Period*. March 1998.

81 Rudkin GE. Local and regional anaesthesia in the adult day surgery patient. In: *Practical Anaesthesia and Analgesia for Day Surgery*. Oxford: BIOS Scientific Publishers, 1997; 207–10

82 Rudkin GE. Pain management in the adult day surgery patient. In: *Practical Anaesthesia and Analgesia for Day Surgery*. Oxford: BIOS Scientific Publishers, 1997; 207–10

83 Rømsing J, Møiniche S, Østergaard D, Dahl JB. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand* 2000; **44**: 672–83

84 Scott NB, Hodson M. Public perceptions of postoperative pain and its relief. *Anaesthesia* 1997; **52**: 438–42

85 Sepponen K, Kokki H, Ahonen R. Training of medical staff positively influences postoperative pain management at home in children. *Pharm World Sci* 1999; **21**: 168–72

86 Stein C, Haimori E, Yassouridis A *et al.* Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *New Engl J Med* 1991; **325**: 1123–6

87 Striebel HW, Oelmann T, Spies C *et al.* Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* 1996; **83**: 548–51

88 Tong D, Chung F. Postoperative pain control in ambulatory surgery. *Surg Clin N Am* 1999; **79**: 401–30

89 Urmey WF. Combined spinal epidural anesthesia. *Tech Reg Anesth Pain Mgmt* 2000; **4**: 13–8

90 Urmey WF, Stanton J, Peterson M *et al.* Combined spinal–epidural anesthesia for outpatient surgery: dose–response characteristics of intrathecal isobaric lidocaine using a 27-gauge Whitacre spinal needle. *Anesthesiology* 1995; **83**: 528–34

91 Vaghadia H. Spinal anaesthesia for outpatients: controversies and new techniques. *Can J Anaesth* 1998; **45**: R64–70

92 Vintar N, Pozlep G, Rawal N, Godec M, Rakovec S. Incisional analgesia by self-administration of local anaesthetic solution on demand after inguinal hernia repair: comparison of bupivacaine and ropivacaine. *Int Monitor Reg Anaesth Pain Ther* 2000; **12**: 257

93 Weinstein MS, Nicholson NC, Schreiner MS. A single dose of morphine sulphate increases the incidence of vomiting after outpatient inguinal surgery in children. *Anesthesiology* 1994; **81**: 572–7

94 White P. Ambulatory anesthesia advances into the new millennium. *Anesth Analg* 2000; **90**: 1234–5

95 Wilson GAM, Doyle E. Validation of three paediatric pain scores for use by parents. *Anaesthesia* 1996; **51**: 1005–7

96 Wolf AR. Tears at bedtime: a pitfall of extending paediatric day-case surgery without extending analgesia. *Br J Anaesth* 1999; **82**: 319–20

97 Woodhouse A, Hobbes AFT, Mather LE, Gibson M. A comparison of morphine, pethidine and fentanyl in the postsurgical patient-controlled analgesia environment. *Pain* 1996; **64**: 115–21

98 Zacharias M, Watts D. Pain relief in children: doing the simple things better. *Br Med J* 1998; **316**: 1552

99 Zohar E, Fredman B, Shapiro A, Philipov A, Jedeikin R. The analgesic efficacy of patient controlled bupivacaine instillation following total abdominal hysterectomy. *Int Monitor Reg Anaesth Pain Ther* 2000; **12**: 250

100 Zohar E, Fredman B, Shapiro A, Rawal N, Jedeikin R. The analgesic efficacy of patient controlled ropivacaine instillation following Caesarean section. *Int Monitor Reg Anaesth Pain Ther* 2000; **12**: 249

101 Zuurmond WWA, Van Leeuwen L. Alfentanil vs isoflurane for out-patient arthroscopy. *Acta Anaesthesiol Scand* 1986; **30**: 329–31

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Chronic pain after surgery

W. A. Macrae

The Pain Service, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

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Chronic pain after surgery has until recently been a neglected topic. The extent of the problem first came to light in a survey of patients attending pain clinics in Scotland and the north of England.[17] This survey showed that about 20% of patients attending chronic pain clinics implicated surgery as one of the causes of their chronic pain and, in about half of these, it was the sole cause. An extensive literature search failed to produce any references on the general topic of chronic pain after surgery. There were, however, almost 400 references on chronic pain after specific operations, such as mastectomy, cholecystectomy and thoracotomy. The information from this literature search formed the basis of a chapter, entitled 'Chronic postsurgical pain',[33] in *Epidemiology of Pain*, edited by I. K. Crombie and published by the IASP Press in 1999.[14] Much of the information in this review is published in greater detail in that chapter and I am grateful to IASP Press for permission to use some of the material included in it.

One of the problems facing anyone reviewing this topic is the quality of the publications. Many of the studies identified by the literature search were of poor quality. For example, in some of the papers the methods section explained how to do the surgical operation but, in some cases, did not clearly identify the number of patients investigated, the definitions used, the follow-up time or the outcome measures. Many of the problems that will be addressed below (see Defining chronic post-surgical pain) were simply ignored in most studies. One of the interesting findings from the literature is that studies which are designed specifically to investigate the incidence of chronic pain after any operation always find a higher incidence than studies in which chronic pain is studied only as part of a much broader investigation. It also has to be said that these broader studies tend to be less well conducted, often with serious methodological flaws.

The content of this review will be as follows. An attempt will be made to define chronic post-surgical pain and to discuss some of the difficulties in reaching a workable definition. The pain syndromes associated with many individual types of operation will be discussed briefly, with reference to some of the publications in each category. Where appropriate, information will be displayed in table form. The management of patients with chronic post-surgical pain will be mentioned, but not reviewed in detail. Lastly, the reasons for the neglect of the subject of chronic post-surgical pain will be explored and some suggestions made about how this could be rectified.

Defining chronic post-surgical pain

Defining when a pain becomes chronic is always difficult. Pain that is unlikely to resolve or pain that lasts longer than the usual healing time have been suggested, as well as various time scales, usually 6 or 3 months.[37] In pain after surgery, there is an added problem because many patients undergo surgery because of a painful condition, such as gallstones or a prolapsed intervertebral disc, and the pre-existing pain will confuse the issue. Is the pain merely a continuation of the pre-surgical problem or is it a new problem? If it is new, is it related to the surgery? In some cases it is obvious that there is a new problem, for example if there is nerve injury after cholecystectomy the pain will be quite different from the pain of gallstones and will be accompanied by sensory changes. In many cases, though, it is difficult to disentangle the pains, especially if the pain that the patient complained of before surgery is not helped by the operation.

In order for pain to be classified as chronic post-surgical pain, the following criteria should be satisfied.[33]

- The pain developed after a surgical procedure.
- The pain is of at least 2 months duration.
- Other causes for the pain should have been excluded (e.g. continuing malignancy or chronic infection).
- The possibility that the pain is continuing from a pre-existing problem must be explored and exclusion attempted. (There is an obvious grey area here in that surgery may simply exacerbate a pre-existent condition, but attributing escalating pain to the surgery is clearly not

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Table 1 Chronic pain after breast surgery. VRS=verbal rating scale; VAS=visual analogue scale; MPQ=McGill pain questionnaire

Study type	Outcomes studied	Source of study subjects	Sample size	Pain measure	Duration of follow-up	Estimated prevalence of symptoms	Reference
Survey	Various	Patient support group volunteers	314 in sample, 251 responses of which 223 usable	Descriptions and VRS	16 months to 32 yr (mean 8 yr)	Phantom breast 36% Numbness 39–78% Paraesthesiae 19–35% Sensitivity 23–34% Pain 22–32%	46
Prospective cohort	Phantom breast pain, scar pain	Oncology and radiotherapy department	120 patients, 110 at 1 yr	Descriptive	1 yr	Phantom breast pain 3 weeks 13% 1 year 13% Scar pain 3 weeks 35% 1 year 23%	30
Prospective cohort	Phantom breast pain, scar pain	Oncology and radiotherapy department	120 patients, 110 at 1 yr, 69 at 6 yr	Descriptive	6 yr	Phantom breast pain at 6 yr 17% Scar pain at 6 yr 31%	29
Retrospective cohort	Pain, strange sensations and paraesthesiae	Breast cancer patients from department of surgery	569 contacted, 467 analysed	VAS, VRS, MPQ and drug use	9–58 months	Pain 49% Paraesthesia 54% 'Strange sensations' 50%	65
Retrospective cohort	Pain	Breast cancer patients from medical centre	479 contacted, 282 responses	VAS, MPQ	2–6 yr	Pain 1 yr after mastectomy 31% Mastectomy/reconstruction 49% Breast augmentation 38% Breast reduction 22%	68
Survey	Pain	Oncology out-patients (grab sample)	95 patients	MPQ and cancer pain questionnaire	Not stated	Post mastectomy pain 20%	61
Survey	Morbidity after axillary dissection	Patients attending breast clinic	126 patients	Not stated	6 months to 4 yr	1 year 45% 1–2 yr 37% 2–4 yr 28% >4 yr 20%	23

possible as natural deterioration cannot be ruled out.) Unfortunately, in most of the published studies no attempt at definition is made. In studies in which a definition is used, it varies from study to study.

Chronic post-surgical pain syndromes

Pain after breast surgery

There are several publications on chronic pain after breast surgery and they vary widely in the design and quality of the studies. The majority of the studies are concerned with pain after surgery for breast cancer, usually mastectomy with or without axillary clearance. Table 1 summarizes the data from some of these studies and shows that morbidity after breast surgery is common and that it persists with time. Several types of pain syndrome are described: phantom breast pain, pain in or around the scar, pain in the chest wall and pain in the arm. Phantom sensations after mastectomy have been studied extensively by Kroner and colleagues.[29 30] The phantoms may be painless but, in many cases, the patient suffers phantom pain after mastectomy, with an incidence varying from about 13% at 3 weeks to 17% at 6 yr. However, these data have to be interpreted with caution as these patients all had breast cancer and there was an inevitable fall in number from 120 to 69 over the 6-yr period. Scar pain in this group of patients remained constant at about 30% over the 6-yr period. It is important to realise that surgery is not the only cause of pain in this group of patients, and Vecht and colleagues[67] found nine different categories of problems in 38 patients who they studied with pain in the arm after mastectomy. In only eight of this group was the pain definitely attributable to nerve injury caused by the surgery. Other causes included brachial plexus neuropathy resulting from infiltration by cancer or radiotherapy, cervical radiculopathy, carpal tunnel syndrome and pericapsulitis of the shoulder joint. Another important finding from this study is related to the timing of the onset of the pain. Post-surgical pain normally developed within the first few weeks after the operation. In contrast, pain from infiltration caused by cancer or radiotherapy normally developed after a median delay of around 5 yr. This pattern of onset was repeated for thoracic surgery and will be discussed further below (see Pain after thoracic surgery).

The nature of the breast surgery influences the incidence of problems. Wallace and colleagues[68] investigated pain after mastectomy, mastectomy with reconstruction, cosmetic augmentation and breast reduction. Almost half of those who had mastectomy with reconstruction had pain at 1 yr compared with only about one-third of those who had mastectomy alone and a quarter of those who had breast reduction. In this study, patients who had implants had a higher incidence of pain (53%) than those who did not (30%). Pain is not the only symptom experienced by these patients, and Polinsky[46] showed that many patients are greatly troubled by numbness, paraesthesia and sensitivity, as well as pain. She also reported considerable morbidity related to chemotherapy and radiotherapy. Tasmuth and colleagues confirmed these findings in a study of 569 women who had undergone modified radical mastectomy with axillary clearance or breast resection with axillary clearance.[65] They reported that about one-third to one-half of the patients suffered from pain, paraesthesia, oedema, strange sensations or muscle weakness. One-quarter of the patients reported a significant effect on their daily lives from these symptoms. This study also showed that those patients who had radiotherapy and chemotherapy as well as surgery had the highest incidence of pain. In a study of 126 women after axillary clearance, who had neither radiotherapy nor chemotherapy, Ivens and colleagues[23] showed that 70% of women complained of numbness, 33% of pain, 25% of weakness, 24% of arm swelling and 15% of stiffness. In 39% of these patients the symptoms affected their daily lives. In a study of 95 women after breast surgery, Stevens and colleagues reported significant interference with the performance of daily occupational and domestic activities.[61] They found that the women were undertreated and had poor pain relief and symptom control.

Not only has the problem of chronic pain after surgery been neglected but Watson and colleagues[69] reported that misdiagnosis is common. In only two of the 18 patients that they studied with post-mastectomy pain syndrome was the correct diagnosis made before referral. Many of the patients were labelled as having 'emotionally derived pain' by the referring physician. The authors used the Beck Depression Inventory to evaluate depression and found that only six of the 18 patients scored in the mildly depressed range. Given that all these patients had breast cancer and chronic pain, it is surprising that the level of depression was not higher. What is depressing is that several years later, articles are still appearing which implicate psychological causes for pain after breast surgery.[54]

Pain after thoracic surgery

When you consider what is involved in a thoracotomy, it is not surprising that many patients suffer long-term pain afterwards. In order to gain access to the chest, the surgeon has to either resect a part of a rib or spread ribs, which inevitably causes mechanical trauma both anteriorly and posteriorly. The intercostal nerves lie along the lower border of the ribs and are liable to injury, which may be quite subtle and need not involve transection. Experience from other pain syndromes suggests that many of the worst pain syndromes are caused by partial nerve injury. Therefore, it is not surprising to find that patients suffer a wide range of symptoms after thoracotomy. The best-recognized pain syndrome after thoracotomy is probably related to injury to the intercostal nerves. This produces a typical neurogenic type of pain syndrome, with both spontaneous and evoked pain, as well as other sensory disturbances. The incidence of pain after thoracotomy has been the subject of several studies and these are summarized in Table 2.

Although pain after thoracotomy is fairly common, the severity varies, and typically 80% of patients scoring 4 or less on a 10-point visual analogue scale.[16] In a large and well-conducted study, Richardson and colleagues found a point prevalence of post-thoracotomy neuralgia of 22% at 2 months and 14% at 12 months. In 15% of these patients, the pain was sufficiently troublesome to require a pain clinic referral.[51]

Again, the timing of the onset of pain can have important implications for causality. Pain related to the operation usually starts in the immediate post-operative period or the first few weeks thereafter. Two studies looking at patients with thoracic cancer have shown that, if the pain starts after a pain-free period or gets worse after an interval of relatively mild pain, the cause is likely to be tumour recurrence.[28 35] The study by Keller and colleagues[28] also suggests that those who have more severe pain before the operation may be more likely to develop chronic pain after the procedure.

Several studies have investigated the influence of post-operative pain control on the development of chronic pain after thoracotomy. In a retrospective study of 90 patients Matsunaga and colleagues[35] found that the proportion of patients who reported chronic pain varied according to their need for analgesia in the acute post-operative period. Of the 32 patients who required analgesia every day during the first 14 days after surgery, 91% had pain at 6 months. In the 45 patients who did not need analgesics every day, only 44% had pain at 6 months. Kalso and colleagues[26] in a retrospective study of 150 patients followed up for 2 yr found that patients with ongoing chronic pain were significantly more likely to report their acute post-operative pain as excruciating and the pain relief provided as being poor. In a prospective study, Katz and colleagues[27] found that early post-operative pain was the only factor that significantly predicted long-term pain. The link between post-operative pain and chronic pain does not necessarily imply causality but is nonetheless interesting and deserves further investigation.

Several studies have investigated different types of thoracotomy. However, inevitably, most of these studies have been quite small and the results must be interpreted with caution. From existing studies, it is not possible to

Table 2 Chronic pain after thoracotomy. VAS=visual analogue scale; VRS=verbal rating scale; MPQ=McGill pain questionnaire

Study type	**Outcomes studied**	**Source of study subjects**	**Sample size**	**Pain measure**	**Duration of follow-up**	**Estimated prevalence of symptoms**	**Reference**
Survey of records	Post-thoracotomy neuralgia	Hospital records: 10-yr period	3109 records	Not stated	≥3 months	5%	11
Retrospective cohort	Post-thoracotomy neuralgia	1000 consecutive patients after thoracotomy	1000 records, 883 analysed	Not stated	≥2 months	Pain at 2 months 22%, pain at 12 months 14%. Severe enough for referral in 15% of patients	51
Retrospective cohort	Post-thoracotomy pain	Hospital records: patients after thoracotomy and video-assisted thoracic surgery	391 contacted, 343 responses	VAS and VRS	>3 months	Pain after lateral thoracotomy <1 yr 44% 1 yr 29% After video-assisted surgery <1 yr 30% >1 yr 22%	31
Retrospective cohort	Post-thoracotomy pain	Hospital records	56 patients	VAS	≥2 months	54% with pain	16
Retrospective cohort	Chest pain	Hospital records: 50 consecutive patients	50 patients	VAS, MPQ and analgesic requirement	Up to 6 months	Pain at 6 months Non-serratus sparing antero- axillary thoracotomy 8% Posterolateral thoracotomy 12%	42
Prospective, randomized, blind trial of cryoanalgesia	Post-thoracotomy pain	60 consecutive thoracotomy patients	53 patients	VAS and analgesic use	6 weeks and 6 months	Pain in cryoanalgesia group 23%, pain in control group 7%	53
Retrospective cohort	Post-thoracotomy pain	Additional phone follow-up of post-thoracotomy patients in trial	30 patients initially, but only 23 contacted	VAS and MPQ	Approximately 1.5 yr after thoracotomy	52% post-thoracotomy pain	27
Retrospective cohort	Post-thoracotomy pain	Medical records of patients who had thoracotomies	214 records, 150 survivors, 134 replies	Analgesic use	≥6 months	44% post-thoracotomy pain	26
Retrospective cohort	Post-thoracotomy pain	238 consecutive patients	238 patients	Pain assessment card; pain impact statement	≥3 months	11% post-thoracotomy pain	28
Retrospective cohort	Post-thoracotomy pain	Surgical records	90 contacted, 77 responses	Not stated	6–18 months	67% post-thoracotomy pain, 20% required medication	35

reach any firm conclusions about whether technique influences long-term pain. It would be expected that thoracoscopic procedures would produce less long-term chronic pain than open procedures. Once again, no clear evidence has emerged on this topic but it is already clear that thoracoscopic procedures still carry a significant long-term morbidity.

Chronic pain after cholecystectomy

Cholecystectomy is a difficult area to investigate because most patients have bouts of pain before surgery and in many patients problems persist after cholecystectomy. Typically, around 40% of patients still complain of problems, many of which relate to pain.[4 52] On the other hand, patients are led to believe by their doctors that their symptoms will be relieved by the operation.[52]

A summary of studies on chronic pain after cholecystectomy is shown in Table 3. Although these studies show a prevalence of chronic pain varying from 3% to more than 20%, they fail to take account of pre-existing problems and, in most cases, the type of pain. Furthermore, the pain measures used are vague or are not described.

It might be expected that laparoscopic cholecystectomy would produce a lower incidence of problems. Although two studies have compared laparoscopic with open cholecystectomy, the results are contradictory and neither of the studies was prospective, randomized nor properly blinded.[62 71] There have been many publications purporting to investigate the safety, efficacy and complications of laparoscopic cholecystectomy, often with quite large

Table 3 Chronic pain after cholecystectomy

Study type	Outcomes studied	Source of study subjects	Sample size	Pain measure	Duration of follow-up	Estimated prevalence of symptoms	Reference
Retrospective cohort	Upper abdominal pain	Hospital patients after open and laparoscopic cholecystectomy	450 contacted, 360 responses	Not stated	Mean follow up: laparoscopic 15 months, open 32 months	Pain after laparoscopic 3.4%, pain after open procedure 10%	62
Survey	Stomach pain	Hospital patients after open and laparoscopic cholecystectomy	315 contacted, 267 responses	Not stated	At least 12 months, mean 14 months	Pain after laparoscopic 7%, pain after open procedure 7%	71
Retrospective cohort	Symptoms after cholecystectomy	Hospital patients after open cholecystectomy	1930 patients	Dyspepsia or abdominal pain similar to pre-operative symptoms	2 – 9 yr	Prevalence of all symptoms 40%, dyspepsia 11%, mild pain 24%, severe pain 6%	6
Prospective cohort	Pain and other symptoms after cholecystectomy	Elective patients scheduled for cholecystectomy	130	Not stated	2 yr	Dull upper abdominal pain 21%	52
Retrospective cohort	Symptoms after cholecystectomy	Hospital patients after open cholecystectomy	1716 patients initially, 862 contacted, 800 analysed	Not stated	4 yr	Prevalence of all symptoms 31%, 4% with severe pain	59
Prospective cohort	Pain after cholecystectomy	Consecutive patients after cholecystectomy	115 patients	Not stated	12 months	Persistent abdominal pain 27%	4

numbers of patients, but most rarely mention long-term complications.

Chronic pain after dental surgery

Two distinct chronic pain syndromes have been reported after dental surgery—post-traumatic dysaesthesia and phantom tooth pain. The incidence of phantom tooth pain after endodontic therapy has been reported as 3%.[34] For other pain syndromes, the incidence has been reported as varying from 5% to 13% (Table 4).[8 32] An interesting finding from the study by Lobb and colleagues[32] was that most patients who suffered chronic pain after dental surgery did not revisit the dental surgeon. This does suggest that many dental surgeons will be underestimating the morbidity of the procedures.

Pain syndromes after amputation

Pain after limb amputation is undoubtedly the best-documented of all the post-surgical pain syndromes. After limb amputation, pain syndromes fall into two broad categories—stump pain (sometimes called residual limb pain) and phantom pain. Phantom pain is the subject of a separate paper in this issue.[41] Pain after amputation is such an important topic that it will be briefly reviewed here as well. The prevalence of stump pain varies widely according to different studies. Pohjolainen found a prevalence of only 5% in a study of amputees attending a prosthetics factory.[45] In a study of US Army veterans, Sherman and colleagues[55] found an incidence of 62%. Patients often report a tender spot on the stump, and this has led many surgeons to perform exploratory operations searching for neuromas or other triggering factors. Patients in the past have frequently had further amputations in the mistaken belief that this would cure the problem. Local operations rarely help stump pain in the long term and sometimes make patients worse or make it more difficult for them to wear a prosthesis.

The reported incidence of phantom limb pain varies from 85% to around 50%.[24 45 55] Carlen and colleagues[9] investigated phantom limb pain in amputees after the Yom Kippur war and found an incidence of 67%. They studied the onset of the phantom pain and found that it was immediate in 12% of patients, came on during the first day in 10%, during the first week in 12%, the second week in 5%, third week in 16% and later than the third weeks in 2%. The remainder of the patients either had no pain or were uncertain about the date of onset. Phantom pain episodes were studied by Sherman and colleagues,[55] who showed that over a quarter of patients suffered phantom pain for more than 15 h a day and one-fifth of patients had pain for 1 h or less. Over a quarter of patients suffered phantom pain on more than 20 days in each month, another quarter suffering phantom pain on between 6 and 20 days per month, half the patients had pain on 5 days per month or less. Information on the severity of phantom pain is contradictory. Some studies describe only mild or moderate pain but others have shown up to 40% of amputees having

Table 4 Chronic pain after dental surgery

Study type	Outcomes studied	Source of study subjects	Sample size	Pain measure	Duration of follow-up	Estimated prevalence of symptoms	Reference
Survey	Phantom tooth pain	Endodontic therapy patients	732 contacted, 463 usable replies	Not stated	Not stated	3%	34
Survey	Pain	Surgical endodontic patients	206 contacted, 118 responses	Not stated	Not stated	5%	8
Prospective cohort	Pain after endodontic treatment	Surgical endodontic patients	198 contacted, 165 responses	Not stated	1 yr	13%	32

severe phantom pain.[45 56] Several studies have looked at the natural history of phantom limb pain and show that, in a patient population, the prevalence of phantom limb pain does not change. However, some patients improve while others become worse. The duration and frequency of phantom limb episodes tend to decrease in the first 6 months but remain stable thereafter.[24]

Many studies have tried to investigate risk factors for developing phantom limb pain, but this topic remains controversial. There is no association with age, sex, site of amputation, reason for amputation, ethnicity or educational level. Two studies have shown no correlation with the use of a prosthesis[24 55] but one study showed that the length of time between the amputation and receiving a prosthesis significantly correlated with phantom limb pain.[60] This study also showed that 91% of those who did not have phantom limb pain used their prosthesis all day whereas only 27% of those who had phantom limb pain used their prosthesis all day. It is impossible to say from this study whether the use of the prosthesis was preventing the phantom limb pain or whether the phantom limb pain was preventing the use of the prosthesis. Three risk factors have been identified—stump pain,[24 38 55] pre-amputation pain[22 24 40] and non-painful phantom sensations.[38]

Phantom pain in children has been a particularly controversial area, some authors claiming that young children do not suffer phantom limb pain and that those with congenital absence of limbs never suffer phantom limb pain. Both these assertions seem to be false. In a study looking at amputation in children,[57] the prevalence of phantom pain after trauma was 12% but in those with cancer it was 48%. Interestingly, in this subgroup, the incidence rose to 74% if the children had chemotherapy before or at the time of amputation, was 44% if the chemotherapy was after the amputation but was only 12% if chemotherapy was not given.

In the past few years, there has been an explosion of interest in changes in the nervous system after amputation. Using sophisticated scanning techniques, it has been demonstrated that the sensory cortex remaps after amputation. Loss of a limb or part of a limb also causes other problems for the central nervous system, which may involve, for example, the visual pathways and the motor control system. It is thought that these changes may contribute to the development of phantom limb pain. There have been some extraordinary reports of temporary resolution of phantom limb pain using virtual limb boxes containing mirrors, where the patient's brain is fooled into thinking that they still have the missing part.[48] Recent research has shown incontrovertibly that there is a central component to pain after amputation even if there may also be peripheral drive. This exciting new work underlines the futility of methods of treatment aimed at the stump or even the peripheral nervous system to try to relieve phantom pain.

Phantom pain has been described after removal of other body parts, such as the rectum,[5 43] breast,[29] tongue,[19] teeth[34] and genitals.[21] It is interesting that despite the fact that circumcision is the commonest operation carried out on males, there are no reports of phantom foreskin in the literature.

Other chronic post-surgical pain syndromes (Table 5)

Chronic pain after hernia repair is well known to all doctors who work in pain clinics. There are many studies on outcome after hernia repair, but most are of poor quality. Many of the studies do not mention pain and few have looked at this syndrome in detail. In a well-designed prospective randomized trial comparing three methods of open repair, Cunningham and colleagues[15] found an incidence of pain at 12 months of 63%, with 12% suffering moderate or severe pain. At 2 yr, 54% of patients had pain, which was moderate or severe in 11%. A prospective study of laparoscopic herniorrhaphy[12] found a 15% incidence of pain with a follow-up period that averaged 9 months. Inguinal hernia repair using mesh has been reported to cause chronic neuralgia, although the incidence is not reported.[20] Numbness can also be a common problem after hernia repairs and has been reported in a quarter of patients at 2 yr.[15]

Chronic pain after orthopaedic surgery has been the subject of very few studies. In particular, long-term follow-up of chronic pain after trauma is neglected. There have been some studies looking at chronic pain after elective

Table 5 Chronic pain after surgery (miscellaneous). VAS=visual analogue scale; LA=local anaesthetic

Study type	Outcomes studied	Source of study subjects	Sample size	Pain measure	Duration of follow-up	Estimated prevalence of symptoms	Reference
Hernia							
Prospective randomized trial of three surgical techniques	Pain	Trial patients receiving hernia repair	315 patients	VAS	6, 12 and 24 months	Pain at 12 months 63% with 12% moderate or severe. Pain at 2 yr 54%, with 11% moderate or severe	15
Prospective study of trans-peritoneal laparoscopic herniorraphy	Pain	Trial patients receiving hernia repair	60 patients	Not stated	Average follow up 9 months	15%	12
Sympathectomy							
Unclear	Neuralgia after phenol sympathectomy	Patient records	1028 patients but 1666 sympathectomies	Not stated	Not stated	Pain after 9% of operations in 15% of patients	50
Survey	Post- sympathectomy neuralgia after open sympathectomy	Patient records	100 patients but 142 operations	Not stated	Not stated	13%	47
Prospective cohort	Post- sympathectomy neuralgia after open sympathectomy	Patients having open sympathectomy	56 patients but 96 operations	Not stated	6 months	35%	49
Prospective cohort	Neuralgia after sympathectomy with phenol or alcohol	Patients having sympathectomy	386 patients	Pain description 'mild to severe'	6 months	Pain after alcohol sympathectomy 40%, pain after phenol 20%	13
Orthopaedic surgery							
Prospective cohort	Prepatellar neuropathy	Patients after open meniscectomy	87 patients	Dysaesthesia in area of operation	6 months	44% at 6 months	63
Prospective trial	Thigh pain after hip replacement	Two types of hip replacement	215 patients	Thigh pain	1 and 2 yr	Pain at 1 yr 13 and 7%, pain at 2 yr 23 and 3%	7
Retrospective cohort	Pain after total hip replacement	Patients after total hip replacement	505 patients	Not stated	Mean 102 months, range 42–171	Pain when sitting 16%, pain when walking 35%	25
Cardiac surgery							
Retrospective cohort	Chest wall pain	Patients after coronary artery bypass grafting	178 patients	Pain affecting daily life or return to work	Minimum 1 yr, maximum 22 months	5–70% depending on site of harvested bypass conduit	18
Rectal amputation							
Survey	Perineal pain	Patients after abdominoperineal resection for rectal cancer	286 contacted, 177 replies	Presence of perineal pain	≥5 yr	12%	5
Retrospective cohort	Phantom pain	Patients after rectal amputation	22 (21 with cancer)	Phantom sensations and pain	Mean 44 months, range 14–90	68% with phantom sensation, 18% with pain	43

orthopaedic surgery. Swanson reported a 44% incidence of dysaesthetic pains around the knee after open meniscectomy.[63] Outcome after joint replacement has been studied widely but chronic pain has rarely been included. In a prospective study looking at two types of hip prosthesis, Burkart and colleagues[7] found incidences of 13 and 7% at 1 yr and 23 and 3% at 2 yr. A retrospective study of over 500 patients after total hip replacement[25] reported an incidence

Table 5 *Continued*

Study type	Outcomes studied	Source of study subjects	Sample size	Pain measure	Duration of follow-up	Estimated prevalence of symptoms	Reference
Vasectomy							
Retrospective cohort	Testicular pain	Hospital records	172 men	Not stated	4 yr	33% chronic discomfort, 15% 'troublesome', 5% sought further medical help	36
Retrospective cohort	Testicular pain	Hospital records	396 men	Not stated	Mean 19 months, range 8–39	5% chronic testicular pain and 10% pain on intercourse	1
Randomized control trial	Testicular discomfort	Men undergoing vasectomy and enrolled in trial	70 men	VAS	1 yr	37%, control group had pain for 2–24 weeks No pain reported in active group (LA)	44

of pain on sitting of 16% and pain on walking of 35%. The patients were followed up for a mean (range) of 102 (42–171) months.

Turner and colleagues[66] reviewed patient outcomes after lumbar spinal fusion operations. Of the 47 articles found, none was a randomized trial. This makes interpretation almost impossible as most of the operations were performed because of pre-existing back or leg pain. Only six of the studies gave details of continuing back pain and only two of chronic leg pain. Surgery for back pain is a controversial area and it is remarkable that the quality of studies is so poor.

There is a fairly extensive literature on pain after lumbar sympathectomy. Post-sympathectomy neuralgia is a syndrome of pain in the thigh, often of a burning nature, which can occur after sympathectomy and typically lasts 2–3 months. The incidence has been variously quoted as 12–35% after both open sympathectomy[47 49] and percutaneous phenol sympathectomy.[13 50] The fact that the incidence is so similar after open and percutaneous sympathectomy suggests that the problem is a result of the sympathectomy itself rather than the technique used to achieve it. In the past, some authors have blamed the spread of phenol from the sympathetic chain posteriorly to the spinal nerve roots for this pain syndrome. There has never been any evidence to support this claim, and the fact that open sympathectomy has the same incidence of post-sympathectomy neuralgia suggests that spread of phenol is not the cause. Fortunately, this syndrome is normally self-limiting, which is in contrast to many of the other pain syndromes following surgical procedures.

Vasectomy is the second most common operation performed on men worldwide. It is performed for social reasons rather than because of illness and men having vasectomies are pain-free before the procedure. It is distressing, therefore, to find that chronic testicular pain occurs in between 5%[1] and 33%[36] of patients. Once again, several different syndromes have been described and the pain may be spontaneous or may occur during intercourse. In an interesting study on the influence of local anaesthesia, Paxton and colleagues[44] injected local anaesthetic on one side but not on the other. They concluded that injecting the local anaesthetic prevented the development of chronic pain after vasectomy. Unfortunately, this finding is not borne out by experience as patients do present to pain clinics with pain after vasectomy performed under local anaesthetic. It is possible that, in these cases, local anaesthesia was incomplete.

Chronic pain after cardiac surgery is another problematical area because many patients present with angina. Differentiating angina from the pain after surgery can be difficult for patients. However, some patients do have a typical dysaesthetic, neurogenic type of pain syndrome and, if veins are harvested from the leg, damage can be caused to the saphenous vein with consequent neurogenic pain in the leg. Eng and Wells[18] reported that the use of the internal mammary artery carried a higher incidence of chronic pain compared with the use of veins.

Pain after prostatectomy, although usually of low intensity, has a reported prevalence of 33% 20 weeks after surgery.[39] Pain after colposuspension was investigated by Wheelan,[70] who found that 27% of patients had pain, which persisted for 2 months or longer but disappeared by 4 months.

The initial pain clinic survey showing an unexpectedly high incidence of pain after surgery[17] reported several patients having pain after hysterectomy. Therefore, it is disappointing that there are no high-quality studies investigating chronic pain after gynaecological surgery.

Clinical presentation and management of chronic post-surgical pain syndromes

Most pain clinicians are moving away from classical diagnostic categories to a more mechanism-based diagnosis in patients with chronic pain. This approach aims to understand the mechanism causing the patient's pain and to direct treatment at that mechanism. For example, if the cause of the pain is a nerve injury, the treatment should be directed at whatever mechanism is thought to be responsible for that neurogenic pain. Sadly, although this approach is probably a step forward, it is still very crude. It does have utility, however, especially in the treatment of this group of patients. Treatment does not depend upon what sort of surgery the patient has had but rather on the mechanism which results in the patient having pain. To this end, the patient's description of the pain is of great importance and the use of such words as tingling, burning and shooting will alert the clinician to the possibility of neurogenic pain, whereas aching or sharp pains with local tenderness may be related to a nociceptive or inflammatory cause. Sensory testing is important, and findings of anaesthesia, allodynia (pain from a stimulus that is not normally painful, such as cotton wool) or hyperalgesia (more pain than one would expect from a painful stimulus, such as a pinprick) should confirm the diagnosis of a neurogenic type of pain. The patient should also be questioned carefully about pre-existing pains. Frequently, patients will tell you that they have had a pain since the operation, but on further questioning, and perhaps on looking at the patient's notes before surgery, one finds that the patient's pain has not changed significantly from before the operation.

The most important aspect of management is to listen to the patient's story, perform a thorough examination and then give a full and frank explanation of the problem. Patients often report finding this approach helpful in itself. Often they feel that, in the past, their symptoms have been dismissed and not taken seriously. Sometimes, patients have been told that the pain will go away soon after the operation (which is at variance with the published data) and this causes mistrust and resentment.

The best treatment for the patient's pain will depend upon the mechanism that is causing it. Neurogenic pain is best treated by tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin or sodium valproate, or a combination of the two. Nociceptive pains can be managed with simple analgesics such as paracetamol or stronger drugs such as weak opioids tramadol or, occasionally, stronger opioids. There is no reliable published evidence on any of these treatments specifically for chronic post-surgical pain but, in essence, the treatment of this type of syndrome is no different from that of other chronic pain syndromes. Transcutaneous electrical nerve stimulation is widely used and can undoubtedly be effective in some cases. It has the advantage of having few side-effects and will not cause any long-term damage. The same cannot be said for ablative techniques. Peripheral nerve ablation has no place in the management of these syndromes and carries an unacceptable morbidity. Local injections of anaesthetic and steroid may be useful but repeated injections of steroids are not without risk.

It is not always possible to control the pain and other symptoms adequately. In such cases, patients will require a psychology-based pain management approach to help them to cope with their problems and reduce the impact on their daily lives. Many patients, for example those with cancer, or patients who have had a mastectomy or a limb amputation, may have special needs.

Reasons for neglect

It is clear from the studies described that chronic post-surgical pain is common, can be severe and results in distress and disability for patients. Why then has this been neglected? In a survey of surgical textbooks, the author found that the general topic of chronic pain after surgery was totally ignored. In many textbooks, chronic pain after operations such as mastectomy, thoracotomy and hernia repair were either mentioned very briefly or ignored altogether. It is hard for any doctor to accept that the treatments they offer may cause morbidity, especially if they feel that they may be to blame. In the past, doctors have often sought to blame patients for diseases that they feel helpless to treat.[3 58]

When one looks at the whole spectrum of the syndromes of chronic pain after surgery, it seems unlikely that the cause of the pain is related to something that the surgeon has done wrong. It seems more likely that this is the inevitable result of surgery in a certain percentage of patients. The author and some other pain specialists feel that certain groups of patients may be more at risk from pain after surgery than others. The patients at higher risk include patients who suffer from such conditions as Raynaud's disease, especially bipolar Raynaud's with erythromelalgia, irritable bowel syndrome, migrainous headaches, fibromyalgia and perhaps several other conditions as well. Changes in the nervous system may well lie behind many of these syndromes. Neural plasticity can result in amplification of sensory input,[10] which may result in somatic or visceral hyperalgesia. This could well have a bearing on chronic post-surgical pain. There is also evidence from animal work that some strains of rat and mice are more likely to develop neurogenic pain after nerve injury than others. It may be that certain people are at particularly high risk of developing pain after surgery. There is evidence that postoperative pain is influenced by psychological and familial factors.[2 64]

Perhaps if it was more widely accepted that chronic pain can arise after surgery, three benefits might result. The first might be that if patients were given accurate data about the incidence of pain after certain operations, some of these patients might decide against having operations that weren't entirely necessary. The second benefit would be that patients would have their pain acknowledged and they would be treated more sympathetically and would not feel blamed in the way that many do at present. It might also benefit surgeons who are undoubtedly trying to do the best for their patients. Patients do not blame their doctor if they develop a side-effect like a rash after taking a drug, as it is accepted that side-effects can occur. If pain after surgery was acknowledged in the same way, it might be easier for everyone.

Conclusions

Chronic pain after surgery has been a neglected topic until recently. A wide variety of operations have been shown to be associated with chronic pain syndromes and it is probable that, for the others, the problem also exists but has merely not been documented. Patients complain of a diverse group of symptoms and management must involve careful attention to each of the problems that the patient suffers. For the longer term, a shift in attitude is required and there is an urgent need for good quality research to try to elucidate risk factors and causes.

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References

1 Ahmed I, Rasheed S, White C, Shaikh NA. The incidence of post-vasectomy chronic testicular pain and the role of nerve stripping (denervation) of the spermatic cord in its management. *Br J Urol* 1997; **79**: 269–70

2 Bachiocco V, Scesi M, Morselli AM, Carli G. Individual pain history and familial pain tolerance models: relationships to post-surgical pain. *Clin J Pain* 1993; **9**: 266–71

3 Balint M. *The Doctor, his Patient and the Illness*. Edinburgh: Churchill Livingstone, 1986

4 Bates T, Mercer JC, Harrison M. Symptomatic gall stone disease: before and after cholecystectomy. *Gut* 1984; **24**: 579–80

5 Boas RA, Schug SA, Acland RH. Perineal pain after rectal amputation: a 5-year follow-up. *Pain* 1993; **52**: 67–70

6 Bodvall B. Late results following cholecystectomy in 1930 cases and special studies on postoperative biliary distress. *Acta Chir Scand* 1964; Suppl: 329

7 Burkart BC, Bourne RB, Rorabeck CH, Kirk PG. Thigh pain in cementless total hip arthroplasty. A comparison of two systems at 2 years follow-up. *Orthop Clin N Am* 1993; **24**: 645–53

8 Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. *Oral Surg Oral Med Oral Pathol* 1990; **69**: 287–90

9 Carlen PL, Wall PD, Nadvorna H. Phantom limbs and related phenomena in recent traumatic amputations. *Neurology* 1978; **28**: 211–7

10 Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–85

11 Conacher ID. Therapists and therapies for post-thoracotomy neuralgia. *Pain* 1992; **48**: 409–12

12 Cornell RB, Kerlakian GM. Early complications and outcomes of the current technique of transperitoneal laparoscopic herniorraphy and a comparison to the traditional open approach. *Am J Surg* 1994; **168**: 275–9

13 Cousins MJ, Reeve TS, Glynn CJ, Walsh JA, Cherry DA. Neurolytic lumbar sympathetic blockade: duration of denervation and relief of rest pain. *Anaesth Intens Care* 1979; **7**: 121–35

14 Crombie IK *et al.* (eds). *Epidemiology of Pain*. Seattle: IASP Press, 1999

15 Cunningham J, Temple WJ, Mitchell P, Nixon JA, Preshaw RM, Hagen NA. Cooperative hernia study. Pain in the post-repair patient. *Ann Surg* 1996; **224**: 598–602

16 Dajczman E, Gordon A, Kreisman H, Wolkove N. Long-term post-thoracotomy pain. *Chest* 1991; **99**: 270–4

17 Davies HTO, Crombie IK, Macrae WA, Rogers KM. Pain clinic patients in northern Britain. *Pain Clin* 1992; **5**: 129–35

18 Eng J, Wells FC. Morbidity following coronary artery revascularisation with the internal mammary artery. *Int J Cardiol* 1991; **30**: 55–9

19 Hanowell S, Kennedy SF. Phantom tongue pain and causalgia: case presentation and treatment. *Anesth Analg* 1979; **58**: 436–7

20 Heise CP, Starling JR. Mesh inguinodynia: a new clinical syndrome after inguinal herniorrhaphy? *J Am Coll Surg* 1998; **187**: 514–8

21 Heusner AP. Phantom genitalia. *Trans Am Neurol Assoc* 1950; **75**: 128–34

22 Houghton AD, Saadah E, Nicholls G, McColl L, Houghton AL. Phantom pain: natural history and association with rehabilitation. *Ann R Coll Surg Engl* 1994; **76**: 22–5

23 Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assesssment of morbidity from complete axillary dissection. *Br J Cancer* 1992; **66**: 136–8

24 Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain* 1985; **21**: 267–78

25 Johnsson R, Thorngren KG. Function after total hip replacement for primary osteoarthritis. *Int Orthop* 1989; **13**: 221–5

26 Kalso E, Perttunen K, Kaasinen S. Pain after thoracic surgery. *Acta Anaesthesiol Scand* 1992; **36**: 96–100

27 Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain* 1996; **12**: 50–5

28 Keller SM, Carp NZ, Levy MN, Rosen SM. Chronic post thoracotomy pain. *J Cardiovasc Surg* 1994; **35** (6 Suppl. 1): 161–4

29 Kroner K, Knudsen UB, Lundby L, Hvid H. Long term phantom breast syndrome after mastectomy. *Clin J Pain* 1992; **8**: 346–50

30 Kroner K, Krebs B, Skov J, Jorgenson HS. Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. *Pain* 1989; **36**: 327–34

31 Landreneau RJ, Mack MJ, Hazelrigg SR, *et al.* Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. *J Thorac Cardiovasc Surg* 1994; **107**: 1079–86

32 Lobb WK, Zakariasen KL, McGrath PJ. Endodontic treatment outcomes: do patients perceive problems? *J Am Dent Assoc* 1996; **127**: 597–600

33 Macrae WA, Davies HTO. Chronic postsurgical pain. In: Crombie IK, ed. *Epidemiology of Pain*. Seattle: IASP Press, 1999; 125–42

34 Marbach JJ, Hulbrook J, Hohn C, Segal AG. Incidence of phantom tooth pain: an atypical facial neuralgia. *Oral Surg Oral Med Oral Pathol* 1982; **53**: 190–3

35 Matsunaga M, Dan K, Manabe FY, Hara F, Shono S, Shirakusa T. Residual pain of thoracotomy patients with malignancy and non-malignancy. *Pain* 1990; (Suppl. 5): S148

36 McMahon AJ, Buckley J, Taylor A, Lloyd SN, Deane RF, Kirk D.

Chronic testicular pain following vasectomy. *Br J Urol* 1992; **69**: 188–91

37 Merskey H, Bogduk N. *Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*, 2nd Edn. Seattle: IASP Press, 1994

38 Montoya P, Larbig W, Grulke N, Flor H, Taub E, Birbaumer N. The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees. *Pain* 1997; **72**: 87–93

39 Niesel T, Partin AW, Walsh PC. Anatomic approach for placement of surgical drains after radical prostatectomy: long-term effects on postoperative pain. *Urology* 1996; **48**: 91–4

40 Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997; **72**: 393–405

41 Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth* 2001; **87**: 107–16

42 Nomori H, Horio H, Fuyuno G, Kobayashi R. Non-serratus-sparing antero-axillary thoracotomy with disconnection of anterior rib cartilage. *Chest* 1997; **111**: 572–6

43 Ovesen P, Kroner K, Ornsholt J, Bach K. Phantom-related phenomena after rectal amputation: prevalence and clinical characteristics. *Pain* 1991; **44**: 289–91

44 Paxton LD, Huss BK, Loughlin V, Mirakhur RK. Intra-vas deferens bupivacaine for prevention of acute pain and chronic discomfort after vasectomy. *Br J Anaesth* 1995; **74**: 612–13

45 Pohjolainen T. A clinical evaluation of stumps in lower limb amputees. *Prosthet Orthot Int* 1991; **15**: 178–184

46 Polinsky ML. Functional status of long-term breast cancer survivors. *Health Soc Work* 1994; **19**: 165–73

47 Postlethwaite JC. Lumbar sympathectomy. *Br J Surg* 1973; **60**: 878–9

48 Ramachandran VS, Hirstein W. The perception of phantom limbs. *Brain* 1998; **121**: 1603–30

49 Raskin NH, Levinson SA, Hoffman PM, Pickett JBE, Fields HL. Postsympathectomy neuralgia. *Am J Surg* 1974; **128**: 75–8

50 Reid W, Kennedy Watt J, Gray TG. Phenol injection of the sympathetic chain. *Br J Surg* 1970; **57**: 45–50

51 Richardson J, Sabanathan S, Mearns AJ, Sides C, Goulden CP. Post-thoracotomy neuralgia. *Pain Clin* 1994; **7**: 87–97

52 Ros E, Zambon D. Post-cholecystectomy symptoms. A prospective study of gall stone patients before and two years after surgery. *Gut* 1987; **28**: 1500–4

53 Roxburgh JC, Markland CG, Ross BA, Kerr WF. Role of cryoanalgesia in the control of pain after thoracotomy. *Thorax* 1987; **42**: 292–5

54 Salmon RJ, Ansquer Y, Asselain B. Preservation versus section of intercostal–brachial nerve in axillary dissection for breast cancer—a prospective randomized trial. *Eur J Surg Oncol* 1998; **24**: 158–61

55 Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: results of a survey. *Pain* 1984; **18**: 83–95

56 Smith DG, Ehde DM, Legro MW, Reiber GE, Aguila MD, Boone DA. Phantom pain, residual limb, and back pain after lower extremity amputations. *Clin Orthop Rel Res* 1999; **361**: 29–38

57 Smith J, Thompson JM. Phantom limb pain and chemotherapy in pediatric amputees. *Mayo Clinic Proc* 1995; **70**: 357–64

58 Sontag S. *Illness as Metaphor*. London: Penguin, 1991

59 Stefanini P, Carboni M, Patrassi N, Loriga P, De Bernadinis G, Negro P. Factors influencing the long term results of cholecystectomy. *Surg Gynecol Obstet* 1974; **139**: 734–8

60 Steinbach TV, Nadvorna H, Arazi D. A five year follow-up study of phantom limb pain in post traumatic amputees. *Scand J Rehabil Med* 1982; **14**: 203–7

61 Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. *Pain* 1995; **61**: 61–8

62 Stiff G, Rhodes M, Kelly A, Telford K, Armstrong CP, Rees BI. Long-term pain: less common after laparoscopic than open cholecystectomy. *Br J Surg* 1994; **81**: 1368–70

63 Swanson AJG. The incidence of prepatellar neuropathy following medial meniscectomy. *Clin Orthop Rel Res* 1983; **181**: 151–3

64 Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. *Pain* 1986; **24**: 331–42

65 Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. *Ann Oncol* 1995; **6**: 453–9

66 Turner JA, Ersek M, Herron L, *et al.* Patient outcomes after lumbar spinal fusions. *J Am Med Assoc* 1992; **268**: 907–11

67 Vecht CJ, Van der Brand HJ, Wajer OJM. Post-axillary dissection pain in breast cancer due to a lesion of the intercostobrachial nerve. *Pain* 1989; **38**: 171–6

68 Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. *Pain* 1996; **66**: 195–205

69 Watson CPN, Evans RJ, Watt VR. The post-mastectomy pain syndrome and the effects of topical capsaicin. *Pain* 1989; **38**: 177–86

70 Wheelan JB. Long-term results of colposuspension. *Br J Urol* 1990; **65**: 329–32

71 Wilson RG, Macintyre IMC. Symptomatic outcome after laparoscopic cholecystectomy. *Br J Surg* 1993; **80**: 439–41

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Complex regional pain syndrome

R. N. Harden

Center for Pain Studies, Rehabilitation Institute of Chicago, 1030 N. Clark Street, Suite 320, Chicago, IL 60610, USA

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Keywords: pain, complex regional pain syndrome

Since the early musings in the mid-1800s of Claude Bernard and his French neurological colleagues on the association of pain with the sympathetic nervous system, complex regional pain syndrome (CRPS) has both fascinated and perplexed practitioners. Some of the clearest and most interesting descriptions of 'causalgia' come from the American Civil War by one of Bernard's students, Silas Weir-Mitchell. The low-velocity, high-mass missiles used in this confrontation (the 'Minnie ball') seemed to be particularly effective in inducing neuropathic pain associated with intense autonomic dysregulation. Weir-Mitchell's depictions are clear and elegant, and as good as any clinical description that can be found in this century.[64] Many great minds have struggled with the pathophysiology of what came to be called 'reflex sympathetic dystrophy' in the later part of the 1900s and what has, since the Orlando consensus-based workshop of 1999, come to be called complex regional pain syndrome (CRPS) (Table 1).[37] [63] [85] From Leriche[46] and his vicious circles we have progressed through Livingston[47] and Sunderland[88] with the turbulence theory, and finally to the solid physiological information generated by the various animal models of causalgia, especially the chronic constriction injury model of Bennett and Xie.[5] Recently, the effort to understand the syndrome has turned towards consensus symposia. The first of these concerned taxonomy, as above.[37] [85] A second Dahlem-type conference was conducted in regard to the guidelines for therapy,[84] and recently the International Association for the Study of Pain (IASP) sponsored a symposium in Cardiff, Wales in 2000 to discuss issues of pathophysiology and to amend the diagnostic considerations.[83]

The epidemiology of the syndrome is very unclear. Although the syndrome has traditionally been considered rare, its 'discovery' by personal injury lawyers in the United States has caused a radical increase in the reporting of the syndrome (at least in the USA). The current diagnostic criteria, as set forth by the Committee of Classification of Chronic Pain of the IASP, have contributed to the liberalization of the diagnosis (Table 1).[63] This effort was extremely important in providing standardized diagnostic criteria, and caused a vast improvement in clinical communication and research homogeneity. It provided the hope that results could be generalized across studies, and in fact widespread use of these standardized criteria has helped all these things considerably. These criteria, while being very sensitive, greatly lack specificity.[9] [21] [31] The intent of the Orlando conference in 1994 was that these criteria should evolve on the basis of experience and empirical testing, and that they should be subject to systematic validation research over time.[37] [62] [85] This has been accomplished to some extent, and through a process of internal and external validation the opportunity to improve the specificity of the bedside diagnostic criteria is available.[9] [21] [31] Although the original IASP criteria required only subjective and potentially only historical signs and symptoms, the suggestions for improving these criteria are that some objectification and observed evidence be included. It is recommended that the diagnostic criteria be modified to include at least one symptom in each of the four diagnostic categories derived by factor analysis: sensory (hyperaesthesia), vasomotor (temperature and/or skin colour asymmetry), sudomotor/oedema (reports of asymmetrical oedema in the affected limb and/or a sweating asymmetry), and a new symptom set which was identified by factor analysis: the motor/trophic set (reports of motor dysfunction or trophic changes).[9] [21] [31] Our data also suggest that the patient should display at least one quasi-objective sign (observed by the physician) in two or more of these categories (Table 2).[9] [31] This approach maintained a sensitivity of 0.70 while increasing specificity to 0.94. This level of specificity is important in research. However, the original IASP criteria could be used if maximal clinical sensitivity was desired. A variety of schemes in which the clinician/researcher can virtually set the sensitivity and specificity, depending on the diagnostic scheme used, have been discussed.[9] [31]

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Table 1 IASP diagnostic criteria for complex regional pain syndrome (adapted from Merskey and Bogduk).[63] *Not required for diagnosis; 5–10% of patients will not have this

1 The presence of an initiating noxious event or a cause of immobilization*
2 Continuing pain, allodynia or hyperalgesia in which the pain is disproportionate to any known inciting event
3 Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain (can be sign or symptom)
4 This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

Table 2 Proposed modified research diagnostic criteria for CRPS (adapted from Bruehl and colleagues[9] and Harden and colleagues[31])

1 Continuing pain that is disproportionate to any inciting event
2 Must report at least one symptom in each of the four following categories:
Sensory: reports of hyperaesthesia
Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry
Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3 Must display at least one sign in two or more of the following categories:
Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry
Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Symptoms

There is great heterogeneity of symptoms endorsed by patients with CRPS.[69] It is essentially a disorder characterized by pain and dysfunction of the sympathetic nervous system. The symptoms most frequently mentioned by patients are spontaneous burning and stinging pain. Although burning pain was an essential part of earlier sets of criteria,[97] it has recently been found to occur in 81.1% of patients meeting criteria for CRPS[31] (all the percentages reported for symptoms and signs in this paper are from this reference). Patients frequently (69%) relate hyperaesthesia in response to the typical mechanical stimuli encountered in their daily lives, such as clothing resting on the affected part, or even draughts blowing on the limb. Patients may relate extreme sensitivity to temperature changes, such as in the environment or in bathing. In CRPS II (which is CRPS associated with major nerve damage[63]), patients may often complain of symptoms appropriate to the neuropathy, such as brief electrical sensations or shooting pain. In this context, they may also demonstrate an interesting presentation of hypo-aesthesia (negative symptom) in the nerve distribution associated with electrical 'shocks' and extreme allodynia (positive symptoms). Other symptoms include asymmetry of the colour or temperature of the affected limb; these are the symptoms most indicative of vasomotor autonomic disturbance (86.9% colour, 78.7% temperature). Sudomotor symptoms can be seen with sweating asymmetry (52.9%), either hyperhidrosis or dryness. Patients may also endorse changes in the skin, nails or hair pattern (trophic changes, 24.4, 21.1 and 18% respectively) and will frequently mention that the limb swells (79.7%) and becomes stiff. Patients frequently also speak of decreased range of motion (80.3%) or loss of motor competence (weakness) in the affected limb (74.6%). They will occasionally notice 'jumping', tremors or myoclonic action in the affected part[77 91] (about 20% each) and symptoms of myofascial pain in the proximal joint.[72]

Signs and tests

The examining physician should seek evidence of altered central processing by looking for allodynia (innocuous stimulation that is now painful, 74%) or hyperpathia (slightly painful stimulation that is now significantly painful and/or painful for a prolonged period). Allodynia should be tested using light touch or brushing of the affected part to see if this elicits pain. Temperature allodynia should be sought. This is most easily tested using warm, cool and ambient-temperature test-tubes of water. The test-tubes are presented in a specific order on the affected part. The patient should mentally subtract the sensation/pain of the ambient tube from the pain associated with the cool or hot tube (subjectively). This is most easily done by assessing pain on a verbal Likert scale (0–10) and recording the spontaneous report, the ambient report and the report of the effect of temperature. These signs can be documented formally by quantitative sensory testing.[19 28 99] The patient may also report pain on movement of the affected joints (with either passive or active movement). Signs of trophic changes of the skin, nails and hair patterns (19.1, 9.3 and 8.5% respectively) should be observed and documented. Signs of autonomic disturbance (temperature asymmetry 56.3%, colour asymmetry 66.4%) need to be measured and described in terms of apparent sympathetic hypofunction (hot, red and dry) or apparent sympathetic hyperfunction (cold, blue, pale or mottled, and sweaty).

Whether these signs accurately reflect activity of the sympathetic nervous system is questionable.[33]

Thermography, or at least a spot-temperature measurement (using a thermosensitive tape or spot-temperature device), best documents vasomotor autonomic disturbance.[10] Abnormal activity of the sudomotor side needs to be assessed clinically using the examiner's touch (24.2%). Dragging a smooth-handled instrument across the affected versus the unaffected part can also give an idea of 'sweatiness' (a smooth-handled instrument will glide more easily over a sweaty area than a dry area). Sudomotor abnormalities can be documented by QSART (quantitative sudomotor axon reflex testing).[48] Decreased range of motion (70.3%), weakness (56.1%), dystonia (14.0%) and tremor (8.8%) can also be seen[77] and myoclonic activity has been observed occasionally.[91] An interesting phenomenon of apparent motor neglect is also observed sometimes.[21] We do not find three-phase bone scans to be particularly helpful (sometimes they are actually confusing!).[45 96] However, we often find sympathetic skin-response testing helps us to define mechanisms better. In some cases the response may be absent or abnormal in early (hot, red, dry) CRPS, but is usually normal in later (cool, blue, sweaty) CRPS.

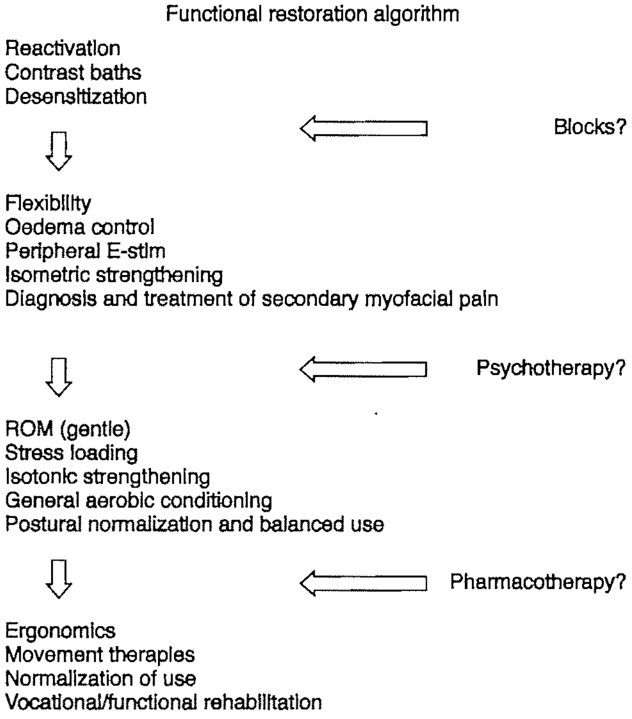

Fig. 1 Steps towards functional restoration. Failure to progress in 2–4 weeks to the next step should cause consideration of more aggressive blocks, psychotherapy and/or pharmacotherapy, depending on the situation. Adapted from Stanton-Hicks.[84]

Treatment

A second Dahlem-type conference was held in Malibu to generate consensus about treatment guidelines.[84] All treatments were focused primarily on functional restoration; the use of drugs, blocks and psychotherapy was reserved for patients failing to progress in the functional algorithm (Fig. 1). Interdisciplinary pain management techniques emphasizing functional restoration are thought to be the most effective therapy; they may work by resetting altered central processing and/or normalizing the distal environment.

The principle of functional restoration is based on steady progression from very gentle movements on an active basis to gentle weight-bearing, such as carrying light bags in upper-extremity syndromes or putting partial weight on the lower extremity in gait training. This progresses to movements that involve more active load-bearing such as the scrub-and-carry techniques of Carlson and Watson.[12 95] Gradual desensitization to increasing sensory stimulus goes along with increased function. This could include such strategies as progressive stimulation with silk, progressing to cloths of other textures, such as towelling, or contrast baths that progressively broaden the temperature difference between the two baths. It is thought that perhaps this gradual increase in normalized sensation tends to reset the altered central processing in the nervous system. It is important to manage oedema, optimize the range of motion and encourage general aerobic activity throughout.[84]

Another basic principle of these functional restoration guidelines is that if patients do not progress through the steps in a reasonable time, then other interventions will be added progressively to give the patient greater comfort or confidence so that they may proceed to the next level. For instance, if the allodynic pain is too great, a sympathetic and/or somatic block may give the patient a window of opportunity to begin to entertain more aggressive therapy or, if the patient has kinesiophobia (fear of movement),[16 17 57] then cognitive behavioural techniques could be undertaken to demonstrate to the patient that movement does not necessarily lead to entirely negative consequences. Neural blockade, psychotherapy and drugs are reserved and should be used only when there is failure to progress.[84]

Occupational therapy

The roles of occupational therapists and physiotherapists differ in many countries. In the USA, the occupational therapists take the lead in functional restoration, and thereby take the lead in the team for treating CRPS.[78] They begin by initiating gentle active movements and preliminary desensitization techniques. Later, they measure and manage the oedema (using volumetry to measure and bandaging and lymph flow massage to manage). They are also responsible for introducing and maintaining a programme of scrubbing/loading.[12 95] The scrubbing can literally be accomplished using a scrubbing-brush, and is usually done with the patient on all fours, putting gradually increasing weight on the arm as they actually scrub in circles. There are technical devices that have been designed for this purpose, but they do not seem to hold any particular advantage over the good oldfashioned scrubbing-brush. A crucial therapeutic point of the scrubbing/loading technique is the weight-loading of the joints in the affected limb, which increases progressively as the scrubbing programme continues. In the upper extremity, the weight-loading part of the treatment continues with small objects carried in the hand, and soon progresses to a handled bag, which can later be loaded with heavier weights.

The lower extremity can be treated with a custom-designed and padded strapping arrangement that attaches a scrubbing-brush like a shoe to the foot. Loading can start in a sitting position, but would gradually progress to standing and putting increasing weight on the foot for brushing. Walking is a relatively advanced loading technique but is clearly one of the most important goals to entertain as early as possible in the treatment of lower extremity CRPS. This therapy may be supplemented by psychology in situations involving post-traumatic stress disorder (PTSD), especially in vocational situations.

Vocational rehabilitation

As the patient progresses, the therapist will begin to work on assessing and simulating work activities. A thorough understanding of the prior job description and requirements, and occasionally vocational testing and targeted retraining, are part of vocational rehabilitation. Eventually, vocational rehabilitation can provide work capacities and targeted work-hardening and functional capacity assessment, so that the patient may return to gainful employment, the ultimate functional restoration. It usually requires a methodical, informed, experienced and organized team approach in order to understand and successfully manage the Byzantine social and medicolegal quagmires CRPS patients may find themselves in. This effort is best orchestrated by vocational rehabilitation.

Physiotherapy

Physiotherapy obviously has an important roll in functional restoration, and the activities in physiotherapy are designed to complement those in occupational and vocational therapy.[78] Beginning with small, gentle active therapies by the patient, the physiotherapist can help the patient begin to extend the range of motion and flexibility through mostly active, gentle activities. These must be done within the patient's tolerance and never in an insensate situation (such as after a block) or in CRPS type II with hypo-aesthesia. Gradually increasing strength and flexibility with ultimate return to normal use is the goal, and this is accomplished by a series of exercises, devices (e.g. foam rubber balls progressing to spring grip strengtheners) and mat exercises. The physiotherapist is also actively involved in gait training and postural correction. It is important to remember that nearly all patients with advanced CRPS will also have myofascial pain syndrome of the supporting joint.[72 87] Aggressive treatment of myofascial pain syndrome is the purview of the physiotherapist, and may be critical to recovery. According to some schools of thought, the myofascial pain syndrome must be treated effectively first; if it is treated the entire syndrome may resolve.[72] Occasionally, hands-on techniques can be used effectively to treat the myofascial pain, such as massage and myofascial release. Desensitization techniques, such as rubbing with silk, then cotton, then towelling or contrast baths, can be very useful. In our experience, electrostimulation modalities may occasionally have some use.[44] Ultrasound and diathermy therapies are less effective in our clinic.[68] The physiotherapist may co-treat with psychology to break through PTSD and kinesophobia.[16 17 42 93]

Recreational therapy

Often the recreational therapist is the first clinician to be able to get the patient to move freely and with some pleasure. In the context of restoring the patient to a pastime or a game that they once enjoyed, it may be possible to break through the kinesophobia and bracing that so often accompany CRPS. With assisted devices and creativity (such as learning to bowl with the non-dominant hand, ride a bicycle instead of run, etc.), a patient can sometimes break the ice and find enjoyment and socialization in previously lost or new recreational activities.

Psychology

Psychology is a critical mainstay of treatment in CRPS, and in some patients may be essential to recovery. There is a high incidence of depression and anxiety in the syndrome,[8 49] and cognitive behavioural psychotherapy is the most effective psychological intervention for these diagnoses in association with chronic pain. In addition to anxiety and depression, there is a high prevalence of post-traumatic stress disorder (PTSD) and what has been called 'kinesophobia'.[8 16 17 49] PTSD is often associated with the initial injury and can prevent full recovery because the patient fears re-encountering the circumstances of their injury.[57 93] Kinesophobia is more an ongoing operant issue associated with negative reinforcement when patients perform particular movements.[42] Patients find that whenever they perform certain manoeuvres they have pain, which acts as a powerful negative reinforcer for performing that movement again. They set up operant patterns that avoid these painful movements, and eventually this avoidance becomes behaviourally set. It is important to demonstrate to patients that the consequences of movement are not always totally negative or painful, and this can be accomplished with a combination of psychotherapy and drug or block therapy.[84] We have learned that normalized movement is critical in the recovery of CRPS patients and a variety of movement therapies, such as the Feldenkrais and Alexander techniques, can be undertaken in the context of psychotherapy. Family therapy can also be quite important, with the basic approach of trying to change solicitous family members into coaches.

Medication

There are many medications that have been reported to be helpful in CRPS, but few that have been tested in double-blind, randomized, controlled trials.[26] At this time, a balanced empirical approach involving observation, consideration of possible mechanisms and the use of the best current information to treat these mechanisms, is the most productive clinical approach. Although monotherapy is the ideal, in practice 'rational polypharmacy' is often employed. This requires a knowledgeable guess as to the mechanisms responsible for the condition, and then combining drugs that make sense together (i.e. an anti-inflammatory and a centrally acting GABAergic agent). Two basic classes of medications should be entertained: drugs used for prophylaxis (used daily) to manage pain and other symptoms, and abortive drugs (drugs used as rescue agents) for crisis management.

The prophylactic drug selected will often be determined by the presentation of the patient. For example, if a CRPS patient is extremely depressed and/or anxious and insomniac, the clinician may choose a tricyclic antidepressant with significant analgesic, sedative and anxiolytic properties as the drug of first choice. The tricyclics are traditional in neuropathic conditions,[54,56,59,94] and seem to be partially effective in CRPS. Good clinicians should have several tricyclic/quadracyclic drugs in their repertoire as they have varied side-effects that can sometimes be used to the patient's advantage.[55,56] Consider the previous example, or consider a patient who is depressed, overweight and hypersomnolent with psychomotor retardation. In such a case it may be useful to select a more noradrenergic agent, such as desipramine, which is activating and may cause some anorexia.[55] Tricyclic and tetracyclic antidepressants have been shown to be effective in other neuropathic conditions, such as post-herpetic neuralgia and diabetic peripheral neuropathy.[10,33,45,48,84,96] However, they have never been studied properly in CRPS.[41] Selective serotonin reuptake inhibitors have been disappointing for CRPS in our experience.[81,82] Certain newer antidepressant agents, such as venlafaxine and mirtazapine, show some benefit in our clinics.

The anti-epileptic compounds are some of the best-studied drugs in neuropathic pain,[58] and currently hold significant promise in the treatment of CRPS. Gabapentin has been studied in large randomized controlled trials in post-herpetic neuralgia and diabetic peripheral neuropathy.[3,74] The research community's attention was originally drawn to gabapentin by an anecdotal report in CRPS (called 'reflex sympathetic dystrophy' in that report).[61] The mechanism of action in Gabapentin may be of interest in CRPS,[13,34] but it is incompletely understood.[73] It probably works primarily by enhancing natural γ-aminobutyric acid (GABA) systems in pain modulation but may also have some impact in suppressing excitatory amino acids, such as glutamate.[29] Other GABAergic drugs have not been tested properly in CRPS.

Membrane-stabilizing anti-epileptic drugs such as phenytoin may have some use, particularly where there is nerve damage or a belief that ectopic activity is involved in generating the pain.[14,53,98] Lamotrigine has been studied in other neuropathic conditions, but randomized controlled trials, especially in CRPS, are lacking. Carbamazepine, which is membrane-stabilizing as well as tricyclic, has a traditional and perhaps clinically important place in the treatment of CRPS, but there are no specific randomized controlled trials.[11,76] Oxcarbazepine may be as effective as carbamazepine but has fewer side-effects.

Non-steroidal anti-inflammatory drugs probably have some role in the management of CRPS, as seen in some other neuropathic models, particularly in cases where there is considerable inflammation.[15,22,35,41,66] Certain drugs in this class may be more useful, such as ketoprofen, which has detectable anti-bradykinin and anti-prostacyclin effects as well as the usual anti-prostaglandin effect. COX-2 inhibitors have not been tested in CRPS. Steroids can be particularly useful in the early/acute phases of CRPS, again particularly when there is significant inflammation. A short course of steroids may be indicated, but longer courses have a questionable risk–benefit ratio.[41]

Opioids may be useful, especially in the acute pain scenario. However, they remain controversial in chronic pain management.[30,41] We have employed a strategy of trying to use non-opioid medication for prophylaxis and using opioids in crisis management. We often tie the use of opioid therapy to increasing function, and may use an acute or subacute opioid protocol to allow the patient to begin to progress in non-pharmacological therapies. Issues of tolerance and long-term toxicity are unresolved as yet[30,32] and there is concern that long-term opioid use may actually elicit allodynia and/or hyperpathia.[51] NMDA receptor antagonists (such as MK-801, ketamine and dextromethorphan) have been considered for management of these effects (and for CRPS), but have proved too toxic for regular human use.[18,52,65,70,89] Low-dose subcutaneous ketamine may have a role.

Many medicines from other fields have proved to be helpful, not only in the management of pain (e.g. clonidine[90]) but also in the management of symptoms associated with CRPS (e.g. nifedipine, which can control the intense vasoconstriction sometimes associated with chronic CRPS). Interestingly, calcitonin is one of the best-studied drugs in the management of CRPS.[7,23,24] Unfortunately, the evidence is mixed and our anecdotal experience with this compound is not particularly encouraging.

The lidocaine patch may be useful in some very local or focal CRPS phenomena, such as patch allodynia.[75] EMLA (eutectic mixture of local anaesthetics) cream has been disappointing in our clinic.[2] Capsaicin has proved to be intolerably painful early on, messy, and thereby to engender very poor compliance, in our experience.[6 25 41 67 80]

While a variety of block therapies have been the traditional first line of treatment in CRPS, there is very little scientific evidence to support their use.[86] We view blocks primarily as providing a pain-free period so that patients may progress in the functional restoration algorithm, and we use them sparingly in that context. Many blocks have been examined, and the most frequently used are paravertebral sympathetic blocks and epidurals.[86] Although it appears clinically that there is excessive sympathetic activity in the later phases of CRPS, the peripheral picture (cold, blue, sweaty extremity) may not actually reflect what is going on in the sympathetic efferents to the limb.[33] Intravenous phentolamine has been reported as useful both therapeutically and diagnostically[1 71] but is not useful therapeutically beyond the placebo effect in our experience.[41 92] Intravenous regional sympathetic blockade using guanethidine[27] or bretylium[41] seem to be more helpful, and have a longer-lasting effect in our patients. The research available is less enthusiastic.[36 41] The use of any of these interventions in a frequent or chronic way has never been justified substantially in the scientific literature. A short trial of a limited number of nerve blocks with very clear goals and time limitations may be indicated ethically and may be cost-effective if the patient fails to progress naturally in a functional restoration effort.

Although sympathectomy has some theoretical support,[4 40 79] it has not shown any long-term benefit in our patients, and may have a negative impact in some cases.[4 20 50] Spinal cord stimulation is of controversial utility and until recently had not been properly studied.[38 43 44 60] A recent randomized controlled trial supports its value in cases where nothing else is helping.[39] Implanted pumps have not been studied properly, and have no long-term utility in our experience.

Conclusions

The key to the successful diagnosis of CRPS is not only to look for and document those historical/subjective elements that meet IASP criteria but also to search for quasi-objective signs (examiner-witnessed). A more specific approach would be to consider the research criteria proposed in Table 2.

The key to successful treatment of CRPS is a trained, coordinated and experienced interdisciplinary team employing a functional restoration approach (Fig. 1). Guidelines help,[84] but creativity, compassion and flexibility are essential. Often patients will require diligent pharmacotherapy, blocks or intensified psychotherapy if they are to make substantial progress.

References

1 Arner S. Intravenous phentolamine test: diagnostic and prognostic use in reflex sympathetic dystrophy. *Pain* 1991; **46**: 17–22

2 Attal N, Brasseur L, Chauvin M, Bouhassira D. Effects of single and repeated applications of a eutectic mixture of local anaesthetics (EMLA) cream on spontaneous and evoked pain in post-herpetic neuralgia. *Pain* 1999; **81**: 203–9

3 Backonja M, Beydoun A, Edwards KR, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *J Am Med Assoc* 1998; **280**: 1831–6

4 Baron R, Maier C. Reflex sympathetic dystrophy: skin blood flow, sympathetic vasoconstrictor reflexes and pain before and after surgical sympathectomy. *Pain* 1996; **67**: 317–26

5 Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988; **33**: 87–107

6 Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol* 1989; **21**: 265–70

7 Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *Br J Rheumatol* 1991; **30**: 291–294

8 Bruehl S, Carlson CR. Predisposing psychological factors in the development of reflex sympathetic dystrophy: A review of the empirical evidence. *Clin J Pain* 1992; **8**: 287–99

9 Bruehl S, Harden RN, Galer BS, *et al.* External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. *Pain* 1999; **81**: 147–54

10 Bruehl S, Lubenow T, Nath H, Ivankovich O. Validation of thermography in the diagnosis of reflex sympathetic dystrophy. *Clin J Pain* 1996; **12**: 316–25

11 Burchiel KJ. Carbamazepine inhibits spontaneous activity in experimental neuromas. *Exp Neurol* 1988; **102**: 249–53

12 Carlson LK, Watson HK. Treatment of reflex sympathetic dystrophy using the stress-loading program. *J Hand Ther* 1988; **1**: 149–54

13 Castro-Lopez JM, Tavares I, Coimbra A. GABA decreases in the spinal cord dorsal horn after peripheral neurectomy. *Brain Res* 1993; **620**: 287–91

14 Chadda V, Mathur M. Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. *J Assoc India* 1978; **26**: 403–6

15 Cohen M, Quintner J. Fibromyalgia syndrome, a protautology. *Lancet* 1993; **342**: 906–9

16 Crombez G, Vervaet L, Lysens R, Eelen P, Baeyens F. Avoidance and confrontation of painful, back straining movements in chronic back pain patients. *Behav Modif* 1998; **22**: 62–77

17 Crombez G, Vlaeyen JWS, Heuts PHTG, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain* 1999; **80**: 329–39

18 Eide PK, Jorum E, Stubhaug A, Brenmes J, Breivik H. Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994; **58**: 347–54

19 Fowler CJ, Carrol MB, Burns D, Howe N, Robinson K. A portable system for measuring cutaneous thresholds for warming and cooling. *J Neurol Neurosurg Psychiatry* 1987; **50**: 1211–25

20 Furlan AD, Mailis A, Papagapiou M. Are we paying a high price for surgical sympathectomy? A systematic literature review of late complications. *J Pain* 2000; **1**: 245–57

21 Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. *Clin J Pain* 1998; **14**: 48–54

22 Gobel H, Stadler T. Treatment of post-herpes zoster pain with tramadol: results of an open pilot study versus clomipramine with or without levomepromazine. *Drugs* 1997; **53**: 34–9

23 Gobelet C, Meier JL, Schaffner W, Bischof-Delaloye A, Gerster JC, Bruckhardt P. Calcitonin and reflex sympathetic dystrophy syndrome. *Clin Rheumatol* 1986; **5**: 382–88

24 Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain* 1992; **48**: 171–5

25 Group CS. Treatment of painful diabetic neuropathy with topical capsaicin: a multicenter, double-blind, vehicle-controlled study. *Arch Intern Med* 1991; **151**: 2225–9

26 Haddox JD, Van Alstine D. Pharmacolgic therapy for reflex sympathetic dystrophy. *Phys Med Rehabil* 1996; **10**: 297–307

27 Hannington-Kieff, JG. Intravenous regional sympathetic blocks. In: Stanton-Hicks M, Janig W, Boas RA, eds. *Reflex Sympathetic Dystrophy*. Boston: Kluwer Academic Publishers, 1989; 113–24

28 Hansson P, Lindblom U. Hyperalgesia assessed with quantitative sensory testing in patients with neurogenic pain. In: Willis WD, ed. *Hyperalgesia and Allodynia*. New York: Raven Press, 1992; 335–43

29 Harden RN. Gabapentin: a new tool in the treatment of neuropathic pain. *Acta Neurol Scand* 1999; **173**: 43–7

30 Harden RN, Bruehl S. Point/counterpoint: the use of opioids in treatment of chronic pain: an examination of the ongoing controversy. *J Back Musculoskel Rehabil* 1997; **9**: 155–80

31 Harden RN, Bruehl S, Galer B, *et al.* Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 1999; **83**: 211–9

32 Harden RN, Bruehl S, Siegler J, Cole PA. *Pain*, psychological status, and functional recovery in chronic pain patients on daily opioids: A case comparison. *J Back Musculoskel Rehabil* 1997; **9**: 101–8

33 Harden RN, Duc TA, Williams TR, Coley D, Cate JC, Gracely RH. Norepinephrine and epinephrine levels in affected versus unaffected limbs in sympathetically maintained pain. *Clin J Pain* 1994; **10**: 324–30

34 Ibuki T, Hama AT, Wang XT, Pappas GD, Sagen J. Loss of GABA immunoreactivity in the spinal dorsal horn of rats with peripheral nerve injury and promotion of recovery by adrenal medullary grafts. *Neuroscience* 1997; **96**: 845–58

35 Jacobson M, Sharma YR, Cotlier E, Hollander JD. Diabetic complications in lens and nerve and their prevention by sulindac or sorbinil: two novel aldose reductase inhibitors. *Invest Ophthalmol Vis Sci* 1983; **24**: 1426–9

36 Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic dystrophy: A systemic review and a randomized, double-blind crossover study. *J Pain Symptom Manag* 1995; **10**: 13–20

37 Janig W, Stanton-Hicks M, eds. *Reflex Sympathetic Dystrophy: A Reappraisal*. Seattle: IASP Press, 1996

38 Kemler MA, Barendse G, Van Kleef M, Van Den Wildenberg F, Weber W. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. *J Neurosurg Spine* 1999; **90**: 79–83

39 Kemler MA, Barendse GAM, van Kleef M, *et al.* Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *New Engl J Med* 2000; **343**: 618–24

40 Kim SH, Chung JM. Effects of sympathectomy on a rat model of peripheral neuropathy. *Pain* 1993; **55**: 85–92

41 Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic and pain complex regional pain syndromes. *Pain* 1997; **73**: 123–39

42 Kori SH, Miller RP, Todd DD. Kinesiophobia: a new view of chronic pain behavior. *Pain Manag* 1990; 35–43

43 Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care* 1997; **20**: 1702–5

44 Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15 year experience. *Neurosurgery* 1997; **40**: 736–46

45 Lee GW, Weeks PM. The role of bone scintigraphy in diagnosing reflex sympathetic dystrophy. *J Hand Surg* 1995; **20A**: 458–63

46 Leriche R. De la causalgie envisagee come une nevrite du sympathique et son traitement per la denudation et l'excision des plexus nerveux periarteriels. *Presse Med* 1916; **24**: 178–80

47 Livingston WK. *Pain Mechanisms: A Physiologic Interpretation of Causalgia and its Related States*. New York: Macmillan, 1944

48 Low P, Caskey P, Tuck R, Fealey R, Dyck P. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 1983; **14**: 573–80

49 Lynch M. Psychological aspects of reflex sympathetic dystrophy: a review of the adult and paediatric literature. *Pain* 1992; **49**: 337–47

50 Mailis A, Furlan AD. Reviewing critically non-controlled literature on surgical sympathectomy: valuable lessons for treating physicians and our patients. *J Pain* 2000; **1**: 265–7

51 Mao J, Price D, Caruso F, Mayer D. Oral administration of dextromethorphan prevents the development of morphine tolerance and dependence in rats. *Pain* 1996; **67**: 361–8

52 Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK-801 and local nerve anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral mononeuropathy. *Brain Res* 1992; **576**: 254–62

53 Matzner O, Devor M. Na^+ conductance and the threshold for repetitive neuronal firing. *Brain Res* 1992; **597**: 92–8

54 Max MB. Thirteen consecutive well-designed randomized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia. *Pain Forum* 1995; **4**: 248–53

55 Max MB, Kishore-Kumar R, Schafer SC, *et al.* Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain* 1991; **45**: 3–9

56 Max MB, Lynch SA, Muire J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326**: 1250–6

57 McCracken LM, Gross RT, Sorg PJ, Edmands TA. Prediction of pain in patients with chronic low back pain: effects of inaccurate prediction and pain-related anxiety. *Behav Res Ther* 1993; **31**: 647–52

58 McQuay H, Carroll D, Jadad AR, Wifen P, Moore A. Anticonvulsant drugs for management of pain: A systematic review. *Br Med J* 1995; **311**: 1047–52

59 McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68**: 217–27

60 Meglio M, Cioni B, Prezioso A, Talamonti G. Spinal cord stimulation (SCS) in the treatment of postherpetic pain. *Acta Neurochir Suppl* 1989; **46**: 65–6

61 Mellick GA, Mellicy LB, Mellick LB. Gabapentin in the management of reflex sympathetic dystrophy. *J Pain Symptom Manag* 1995; **10**: 265–6

62 Merikangas KR, Dartigues JF, Whitaker A, Angst J. Diagnostic criteria for migraine: a validity study. *Neurology* 1994; **44**: S11–S16

63 Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of*

Chronic Pain Syndromes and Definitions of Pain Terms. Seattle: IASP Press, 1994

64 Mitchell SW. *Injuries of the Nerves and their Consequences*. Philadelphia: J. B. Lippincott, 1872

65 Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; **48**: 1212–8

66 Parry GJ, Kozu H. Piroxicam may reduce the rate of progression of experimental diabetic neuropathy. *Neurology* 1990; **40**: 1446–9

67 Peikert A, Hentrich A, Echs G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: efficacy, predictors of response and long-term course. *J Neurol* 1991; **238**: 452–6

68 Portwood MM, Lieberman JS, Taylor RG. Ultrasound treatment of reflex sympathetic dystrophy. *Arch Phys Med Rehabil* 1987; **68**: 116–7

69 Price D, Bennett GJ, Rafii A. Psychophysiological observations on patients with neuropathic pain relieved by sympathetic block. *Pain* 1989; **36**: 273–88

70 Qian J, Brown SD, Carlton SM. Systemic ketamine attenuates nociceptive behaviors in a rat model of peripheral neuropathy. *Brain Res* 1996; **715**: 51–62

71 Raja SN, Treede RD, Davis KD, Campbell JN. Systemic alpha-adrenergic blockage with phentolamine: a diagnostic test for sympathetically maintained pain. *Anesthesiology* 1991; **74**: 691–8

72 Rashiq S, Galer BS. Proximal myofascial dysfunction in complex regional pain syndrome: a retrospective prevalence study. *Clin J Pain* 1999; **15**: 151–3

73 Rosenberg JM, Harrell C, Ristic H, Werner R, de Rosayro AM. The effect of gabapentin on neuropathic pain. *Clin J Pain* 1997; **13**: 251–5

74 Rowbotham M, Harden N, Stacey B, Bernstein P, Mangus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *J Am Med Assoc* 1998; **280**: 1837–42

75 Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for postherpetic neuralgia. *Pain* 1996; **65**: 38–44

76 Rull J, Quibrera R, Gonzalez-Millan H, Lozano CO. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine: double-blind crossover study. *Diabetologia* 1969; **5**: 215–20

77 Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. *Neurology* 1990; **40**: 57–61

78 Severens JL, Oerlemans HM, Weegels A, van't Hof MA, Oostendorp R, Goris JA. Cost-effectiveness analysis of adjuvant physical or occupational therapy for patients with reflex sympathetic dystrophy. *Arch Phys Med Rehabil* 1999; **80**: 1038–43

79 Shir Y, Seltzer Z. Effects of sympathectomy in a model of causalgia from pain produced by partial sciatic nerve injury in rats. *Pain* 1991; **45**: 205–13

80 Simone DA, Ochoa J. Early and late effects of prolonged topical capsaicin on cutaneous sensibility and neurogenic vasodilation in humans. *Pain* 1991; **47**: 285–94

81 Sindrup SH, Bjerre U, Dejgaard A, Brosen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992; **52**: 547–52

82 Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; **42**: 135–44

83 Stanton-Hicks M. A report on the 2nd IASP Research Symposium, Cardiff, Wales. Complex regional pain syndrome: current research on mechanisms and diagnosis. In: International Association for the Study of Pain. *Special Interest Group on Pain and the Sympathetic Nervous System* 2000; 1–2

84 Stanton-Hicks M, Baron R, *et al.* Consensus report: complex regional pain syndromes: guidelines for therapy. *Clin J Pain* 1998; **14**: 155–66

85 Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995; **63**: 127–33

86 Stanton-Hicks M, Raj P, Racz G. Use of regional anesthetics for diagnosis of reflex sympathetic dystrophy and sympathetically maintained pain: a critical evaluation. In: Janig W, Stanton-Hicks M, eds. *Reflex Sympathetic Dystrophy: A Reappraisal. Progress in Pain Management and Research*. Seattle: IASP Press, 1996; 217–37

87 Starlanyl DJ. *The Fibromyalgia Advocate*. Oakland, CA: New Harbinger Publications, 1999

88 Sunderland S. Pain mechanisms in causalgia. *J Neurol Neurosurg Psychiatry* 1976; **39**: 471–80

89 Tal M, Bennett GJ. Dextrorphan relieves neuropathic heat-evoked hyperalgesia. *Neurosci Lett* 1993; **151**: 107–10

90 Tracey DJ, Cunningham JE, Romm MA. Peripheral hyperalgesia in experimental neuropathy: mediation by alpha-2 andreno-receptors on post-ganglionic sympathetic terminals. *Pain* 1995; **60**: 217–327

91 van der Laan L, Veldman P, Goris JA. Severe complications of reflex sympathetic dystrophy: infection, ulcers, chronic edema, dystonia, myoclonus. *Arch Phys Med Rehabil* 1998; **79**: 424–9

92 Verdugo RJ, Campero M, Ochoa JL. Phentolamine sympathetic block in painful polyneuropathies. II. Further questioning of the concept of 'sympathetically maintained pain'. *Neurology* 1994; **44**: 1010–4

93 Vlaeyen JWS, Kole-Snijders AMJ, Rotteveel A, Ruesink R, Heuts PHTG. The role of fear of movement/(re)injury in pain disability. *J Occup Rehabil* 1995; **5**: 235–52

94 Watson CPN, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. *Pain* 1992; **48**: 29–36

95 Watson HK, Carlson L. Treatment of reflex sympathetic dystrophy of the hand with an active 'stress loading' program. *J Hand Surg* 1987; **12A**: 779–85

96 Werner R, Davidoff G, Jackson D, Cremer S, Ventocilla C, Wolf L. Factors affecting the sensitivity and specificity of the three-phase technetium bone scan in the diagnosis of reflex sympathetic dystrophy syndrome in the upper extremity. *J Hand Surg* 1989; **14A**: 520–23

97 Wilson PR. Sympathetically maintained pain: diagnosis, measurement, and efficacy of treatment. In: Stanton-Hicks M, ed. *Pain and the Sympathetic Nervous System*. Norwell, MA: Kluwer Academic Publishers, 1990

98 Yaari Y, Devor M. Phenytoin suppresses spontaneous discharge in rat sciatic nerve neuromas. *Neurosci Lett* 1985; **4**: 117–22

99 Yamitsky D, Sprecher E. Different algorithms for thermal threshold measurement. In: Biovi J, Hansson P, Linblum U, eds. *Touch, Temperature and Pain in Health and Disease: Mechanisms and Assessments. Progress in Pain Research and Management, Vol. 3*. Seattle: IASP Press, 1994; 105–12

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Phantom limb pain

L. Nikolajsen[1 3*] and T. S. Jensen[2 3]

Departments of [1]Anaesthesiology, [2]Neurology and [3]Danish Pain Research Centre, Aarhus University Hospital, DK-8000 Aarhus C, Denmark

**Corresponding author*

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The first medical description of post-amputation sensation was given by Ambroise Paré (1510–1590), a French military surgeon, who noticed that patients may complain of severe pain in the missing limb following amputation. In his 'Haquebusses and other guns', Paré characterized the post-amputation syndrome and proposed different models to explain the pain.[45] Subsequent studies by Charles Bell (1830), Magendie (1833), Rhone (1842), Guéniot (1861) and others provided detailed descriptions of the phenomenon and, in 1871, Mitchell coined the term 'phantom limb'.[26 57 98]

In modern times, traumatic amputations originating from World War I and II, Vietnam and Israeli wars and from landmine explosions all over the world are a tragic cause of phantom pain in otherwise healthy people. Other major reasons for amputation and phantom pain are peripheral vascular disease and neoplasms. Today, it is common knowledge that virtually all amputees experience phantom sensations, painful or not, after limb amputation. Non-painful phantom sensations rarely pose a clinical problem. However, in some amputees, the phantom becomes the site of severe pain, which may be exceedingly difficult to treat. A large number of different treatments have been suggested but the vast majority of studies concerning the treatment of phantom pain are based on small groups with no controls. A clear and rational treatment regimen is difficult to establish as long as the underlying patophysiology is not fully known. The development of animal models mimicking neuropathic pain, together with research in other neuropathic pain conditions, have contributed significantly to our understanding of phantom pain. It is now clear that nerve injury is followed by a series of changes in the peripheral and the central nervous system and that these changes may play a role in the induction and maintenance of chronic phantom pain. Although phantom pains may occur following amputation of body parts other than limbs,[27 49 66] the present review will focus on clinical characteristics, mechanisms, treatment, and possible preventive measures of phantom pain after limb amputation. The phantom complex includes three different elements.

- *Phantom limb pain:* Painful sensations referred to the absent limb.
- *Phantom limb sensation:* Any sensation in the absent limb, except pain.
- *Stump pain:* Pain localized in the stump.

These elements often coexist in each patient and may be difficult to separate.

Clinical aspects

Incidence

Early literature suggested that the incidence of phantom pain was as low as 2%. However, more recent studies report incidences of 60–80% (Table 1). The discrepancy in reported frequencies mainly occurred because early studies based prevalence rates on patients' request for pain treatment. This will substantially underestimate the problem of phantom pain as many amputees, at least in the past, were reluctant to report pain to health care providers. Sherman and Sherman (1983) reported that, although 61% of amputees with phantom pain had discussed the problem with their doctor, only 17% were offered treatment and a large proportion of the rest were told that they were mentally disturbed.[80]

The occurrence of phantom pain seems to be independent of age in adults, gender and level, or side of amputation.[37 46 54 59 80] Phantom pain is less frequent in young children and congenital amputees. In a recent study of 60 child and adolescent amputees who were missing a limb because of congenital limb deficiency (n=27) or surgery/trauma (n=33), the incidence of phantom pain was 3.7% in the congenital group and 48.5% in the surgical group.[99] Some authors have suggested a relationship between

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Table 1 Incidence of phantom pain as reported in different studies

Year, authors	Patients (*n*)	Incidence (%)
1941, Riddoch	?	50
1948, Henderson and Smyth	300	4
1969, Appenzeller and Bicknell	34	56
1973, Parkes	46	61
1978, Carlen and colleagues	73	67
1983, Jensen and colleagues	58	72
1983, Sherman and Sherman	764	85
1985, Wall and colleagues	25	88
1991, Pohjolainen	124	59
1994, Houghton and colleagues	176	78
1995, Krane and Heller	24	83
1997, Wartan and colleagues	526	55
1997, Montoya and colleagues	32	50
1997, Nikolajsen and colleagues	56	75
1998, Wilkins and colleagues.	33	49
2000, Kooijman and colleagues	72	51

phantom limb pain and the aetiology of the amputation.[30 67 96] In a study of 92 lower limb amputees, Weiss and Lindell found that patients with a history of gangrene and/or infection had higher pain levels.[96] However, most studies have found no relationship between the amputees health status and incidence of phantom pain. It is also generally agreed that the incidence of pain is similar following civilian or military accidents.[32 37 59 81]

Onset and duration

Onset of pain is early. Several studies have show that 75% of patients develop pain within the first few days after amputation.[9 37 48 59 67] However, phantom pain may be delayed for months or years. Rajbhandari and colleagues described a 58-yr-old man, who had undergone left below knee amputation at the age of 13. Eight months before a diagnosis of diabetes, he began to complain of typical diabetic neuropathy pain in the phantom leg, which was followed by a similar pain complaint in the intact limb.[72]

At least three prospective studies have examined the duration of phantom pain. Parkes found that 85% of 46 amputees experienced phantom pain immediately post-amputation. One year later, 61% still had some pain.[67] Jensen and colleagues (1985) studied 58 amputees and found that the incidence of phantom pain was 72, 65 and 59% after 1 week, 6 months and 2 yr, respectively.[38] In a recent study by Nikolajsen and coworkers (1997) 56 patients who underwent amputation of the lower limb (mainly because of peripheral vascular disease) were questioned about phantom pain 1 week, and 3 and 6 months after the operation. Although the incidence and intensity of pain remained constant during follow-up, both frequency and duration of pain attacks decreased significantly.[59] Similar results have been found in retrospective studies based on questionnaires. Houghton and collaborators asked 176 amputees to specify on a scale of 0 to 10 the degree of phantom pain at 6 months, 1, 2 and 5 yr after amputation. The median phantom pain score decreased from 4 (moderate) immediately after amputation to 1 (slight), 5 yr postoperatively.[32] In a survey of 526 veterans with longstanding amputations, phantom pain had disappeared in 16%, decreased markedly in 37%, remained similar in 44% and increased in 3% of respondents reporting phantom pain.[93]

Character and localization

Phantom pain is usually intermittent; only a few patients are in constant pain.[46 59 93] Kooijman and colleagues studied 99 upper limb amputees of which 37 experienced phantom pain. Nine amputees were in constant pain, nine had attacks of pain a few times per day and the rest only experienced phantom pain weekly or less.[46] Phantom pain is described as shooting, stabbing, boring, squeezing, throbbing, and burning. A few patients more vivid and colourful descriptions.[9 37 38 42 54 59 93]

Phantom pain is primarily localized in distal parts of the missing limb (fingers and palms in upper limb amputees and toes, instep, top of the foot and ankle in lower limb amputees).[38 59]

Pre-amputation pain and phantom pain

Several retrospective studies—but not all[29 46 92]—have pointed to pre-amputation pain as a risk factor for post-operative phantom pain.[3 32 42 75] In paediatric amputees, Krane and Heller found that most children with phantom pain also experienced pre-operative pain.[48] In the study by Houghton and colleagues there was a significant relationship, in vascular amputees, between pre-amputation pain and phantom pain in the first 2 yr after amputation. In traumatic amputees phantom pain was only related to pre-amputation pain immediately after the amputation.[32] Similar findings have been described in prospective studies.[38 59] In the recent study of mostly vascular amputees by Nikolajsen and colleagues, a relationship was found between pre-operative pain and incidence of phantom pain 1 week and 3 months after amputation, but not after 6 months. However, as can be seen from Figure 1, the relation is not simple. Some patients with severe pre-amputation pain never developed phantom pain while others with only modest pre-operative pain developed intense phantom pain.[59]

Another issue concerns the possible persistence or revival of pain experienced before amputation. Striking case reports show that phantom pain may mimick pre-amputation pain both in quality and in location.[5 29 31 42 56 59] A recent study describes a woman who had her left leg amputated because of recurrent wound infection over a period of 2 yr. The most distressing pre-operative pain was invoked by the treatment carried out on the open drainage site on the calf, which required cleaning and re-packing twice daily. Immediately after amputation the patient experienced phantom pain

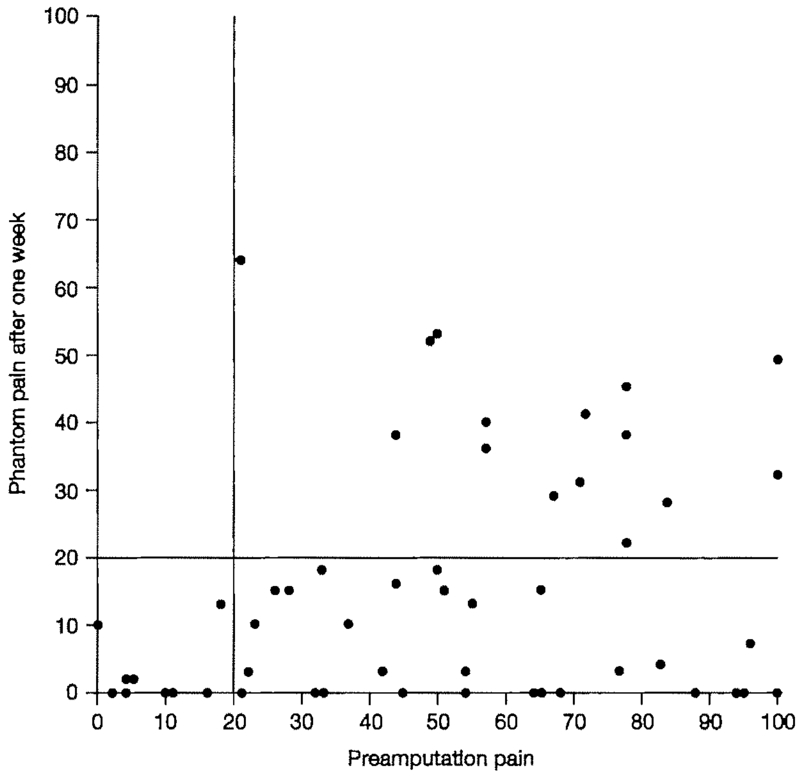

Fig 1 Pre-amputation pain ≥20 increases the risk of phantom pain ≥20 after 1 week and 3 months (on a VAS, 0–100). Data from the 1 week interview are shown. Each dot represents one patient, n=54. P=0.04, Fishers' exact test. (From Nikolajsen and colleagues 1997, with permission).

localized to the open drainage site, which was no longer there. The patient continued to suffer from episodes of phantom pain similar to the pain experienced pre-operatively for several years after the amputation.[31]

In a retrospective study by Katz and Melzack, 68 amputees were questioned about pre-amputation and phantom pain from 20 days to 46 yr after amputation. Fifty-seven of those who had experienced pre-amputation pain claimed that their phantom pain resembled the pain they had before amputation.[42] Jensen and colleagues prospectively examined the incidence of pre-amputation pain persisting as phantom pain. A similarity between pre-amputation pain and phantom pain, with respect to both character and location, was found in one-third of patients after 8 days, but only in 10% of patients after 6 months and 2 yr.[38] In another, more detailed prospective study by Nikolajsen and colleagues, patients were requested to describe pain and its localization before amputation. This was done using different word descriptors, the McGill Pain Questionnaire and their own words. After amputation, 42% of those who experienced phantom pain felt that the pain was similar to the pain they had experienced before amputation. However, when comparing preoperative and postoperative pain descriptions, the incidence of *actual* similarity was not higher in patients who claimed similarity than in those who found their phantom pain did not resemble pain experienced preoperatively. This indicates that patients memory of their pain does not always reflect the truth.[59] So, while a few case reports suggest that pre-amputation may persist as post-amputation pain, this is not the case in the vast majority of amputees.

Stump pain

Not surprisingly, stump pain is common in the early post-amputation period but, in most patients, it subsides with healing. However, in 5–10%, stump pain persists and may even get worse with time. Stump and phantom pain are interrelated phenomena and several authors have reported a higher prevalence of phantom pain among amputees with coexistent stump pain compared with amputees without stump pain.[9 37 38 46 59 80] Examination of the stump frequently reveals factors that may be related to pain. These include obvious pathology such as infection, bone spurs, neuromas and adherent and wrinkled scars. Further examination may reveal reduction in pain threshold (hyperalgesia), evocation of pain by non-noxious stimuli (allodynia) and pain elicited by repeated pricking stimuli ('wind-up' like pain).[9 37 38 62 71] Persistent stump pain may be very difficult to treat and it often interferes with prosthetic use and rehabilitation.

Phantom sensation

Phantom sensation is experienced by almost everyone who undergoes limb amputation, but it is rarely a clinical

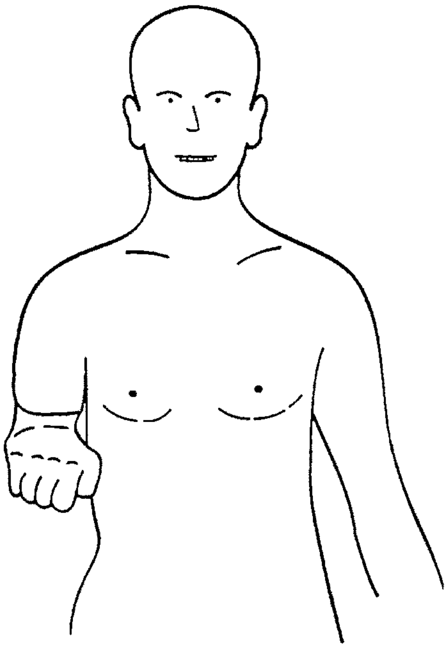

Fig 2 Telescoping. The phantom hand gradually approaches the residual limb and eventually becomes located inside the stump.

problem. Immediately after amputation, the phantom limb often resembles the pre-amputation limb in shape, length, and volume. The sensation can be very vivid and often includes feelings of posture and movement. Over time, the phantom sensation may fade. In some patients, a phenomenon called 'telescoping' occurs when the distal part of the phantom is gradually felt to approach the residual limb and, in the end, it may even be experienced within the stump.[37 38 46 54 93] An example of telescoping is shown in Figure 2. Phantom sensation and phantom pain are interrelated. In a recent study by Kooijman and colleagues, phantom pain was present in 36 of 37 patients experiencing phantom sensation but only in one of 17 who did not experience phantom sensations. Stump pain is also more frequent in patients with coexistent phantom sensation.[46]

Other factors

Evidence is growing that the individual's genetic predisposition to develop neuropathic pain may be important.[53] However, an inherited component is not always a feature of phantom pain. Schott described an interesting case in which five members of a family sustained traumatic amputations of their limbs. The development of phantom pain was unpredictable.[77]

It has been claimed that severe phantom pain may recur in lower-limb amputees undergoing spinal anaesthesia. Tessler and Kleiman prospectively investigated 23 spinal anaesthetics in 17 patients. Only one patient developed phantom pain, which resolved in 10 min.[88]

Phantom phenomena may be modulated be several other internal and external factors, such as stress, attention, urination, stump massage, and weather change. In a group of upper extremity amputees, Weiss and colleagues found that phantom pain was decreased by the use of a prosthesis, which allowed extensive use of the affected limb. A cosmetic prosthesis had no effect.[97] Successful rehabilitation may reduce the amount of pain.[69] A list of modulating factors is shown in Table 2.

Table 2 Factors that may modulate the experience of phantom pain

Internal factors	Genetic predisposition Anxiety/emotional distress Attention/distraction Urination/defaecation Other disease (cerebral haemorrhage, prolapsed intervertebral disc)
External factors	Weather change Touching the stump Use of prosthesis Spinal anaesthesia Rehabilitation Treatment

Mechanisms of phantom pain

The mechanisms underlying phantom pain have not been clarified completely. However, experimental and, to some extent, also clinical studies have contributed to our understanding of phantom pain after amputation. There is now evidence for peripheral and central contributions to phantom pain, as briefly outlined below. An understanding of the mechanisms underlying phantom pain is likely to lead to new and rational types of treatments.

Peripheral factors

1. Phantom pain is significantly more frequent in those amputees with long-term stump pain than in those without persistent pain.[9 37 38 46 59 67 80] It has been noted that phantom pain decreases with the resolution of stump-end pathology.[9]
2. Following a nerve cut, formation of neuromas are seen universally. Such neuromas show spontaneous and abnormal evoked activity following mechanical or chemical stimulation.[2 91] (for review[17]) The ectopic and increased spontaneous and evoked activity from the periphery is assumed to be the result of a novel expression or upregulation of sodium channels.[15 63]
3. Percussion of the stump or of identified stump neuromas induces stump and phantom pain. In a classical microneurographic study in two amputees, Nyström and Hagbarth showed that tapping of neuromas was associated with increased activity in afferent C fibres and increased pain sensation.[64] Consistent with these findings, a recent study shows that there is an inverse correlation between phantom pain intensity and pressure pain threshold of the stump early after amputation.[62]

4. Chabal and colleagues[10] showed that perineuromal injection of gallamine, which increases sodium conductance, produces phantom pain in amputees. However, lidocaine (an unspecific sodium channel blocker), when injected into the neuroma or surrounding tissue, blocks phantom pain.[10]

5. Also, in the dorsal root ganglion (DRG) cells, changes occur following a complete nerve cut. Cell bodies in DRG cells show similar abnormal spontaneous activity and increased sensitivity to mechanical and neurochemical stimulation.[39] DRG cells exhibit major changes with respect to the expression of sodium channels with a switch of one channel type to another.[95]

6. The sympathetic nervous system may also play an important role in generating and, in particular, in maintaining phantom pain. From animal studies, it is well known that application of norepinephrine or activation of the post-ganglionic sympathetic fibres excites and sensitizes damaged but not normal nerve fibres.[16] Sympatholytic blocks can abolish neuropathic pain and, in patients with pain relieved after a sympatholytic block, pain can be rekindled by injection of norepinephrine into the skin.[89] Long after limb amputation, injection of norepinephrine around a stump neuroma is reported to be intensely painful.[11] Catecholamine sensitivity may also manifest itself by the occurrence of a cooler extremity on the amputated side and it has been suggested that phantom pain intensity is inversely related to skin temperature of the stump.[44 82 83]

Spinal plasticity

- Sensitization of spinal pain transmission neurons is a normal physiological response of the undamaged nervous system. After nerve injury, there is an increase in this general excitability of spinal cord neurons, and C-fibres and Aδ-afferents gain access to secondary pain signalling neurons. Sensitization of dorsal horn neurons is mediated by release of glutamate and neurokinins. This sensitization may manifest itself as mechanical hyperalgesia and an expansion of peripheral receptive fields [for review[19]].
- While some amputees may show an abnormal superficial sensitivity to touching the stump, this is rarely sufficient to evoke phantom pain. On the other hand, pressure can often provoke phantom pain. The pharmacology of spinal sensitization involves increased activity in N-methyl D-aspartate (NMDA) receptor operated systems and many aspects of the central sensitization can be reduced by NMDA receptor antagonists.[19] In human amputees, for example, the stump or phantom pain evoked by repetitive stimulation of the stump ('wind-up' like pain) can be reduced by the NMDA antagonist ketamine.[58]
- Another type of anatomical reorganization, which also may produce dynamic mechanical allodynia, has been described recently. Neurons in lamina II normally receive A delta- and C-fibre input and respond best to noxious stimulation. Peripheral nerve damage may result in a substantial degeneration of C-fibre primary afferent terminals in laminae II. As a consequence of this loss of synaptic contacts normally made by C-fibre afferents onto pain signalling neurons in lamina II, central terminals of Aβ-mechanoreceptive afferents, which normally terminate in deeper laminae (III and IV), sprout into laminae I and II.[100] To what extent this spinal reorganization contributes to phantom pain is not known. But the fact that some patients do not show marked changes in stump sensitivity despite considerable phantom pain may be consistent with such spinal reorganization.

Cerebral reorganization

- The phantom limb percept, with its complex perceptual qualities and its modification by a variety of internal stimuli (e.g. attention, distraction or stress), shows that the phantom image may be a product of the brain.
- Electrophysiological studies have documented the existence of nociceptive specific neurons and wide dynamic range neurons in the cerebral cortex. Following limb amputation and deafferentation of adult monkeys, there is a reorganization of the primary somtosensory cortex, subcortex and thalamus.[24] After dorsal rhizotomy, a lowered threshold required to evoke activity in thalamus and cortex can be demonstrated. Also, adult monkeys display cortical reorganization in which the mouth and chin invade cortices corresponding to the representation of the arm and digits which have lost their normal afferent input.[18]
- In humans, similar reorganization has been observed using magnetoencephalographic techniques. Interestingly, this cerebral reorganization was seen mostly in patients with phantom pain and there was a linear relationship between pain and degree of reorganization.[25] Changes have also been observed at more subcortical levels. Using neuronal recording and stimulation techniques, Davis and colleagues found an unusually large thalamic stump representation.[13]

Summary of mechanisms

The above findings indicate that a series of mechanisms are involved in generating phantom pains and that these include elements in the periphery, spinal cord and brain. It is likely that the first events occur in the periphery, which subsequently generates a cascade of events that sweep more centrally and also recruit cortical brain structures. The latter may be reponsible for the complex and vivid sensation that characterizes certain phantom pain sensations. The unraveling of neuroplastic changes in periphery, spinal cord, and brain are also reflected in many of the features seen in phantom pain phenomena.

Table 3 Treatments for phantom pain

Medical	Non-medical	Surgical
TCA	TENS	Neurectomy
Anticonvulsants	Acupuncture	Stump revision
Lidocaine/mexiletine	Bio-feedback	Rhizotomy
Opioids/tramadol	Hypnosis	Cordotomy
NMDA receptor antagonists	Massage	Tractotomy
Beta-blockers	Ultrasound	DREZ lesion
Calcitonin	Electroconvulsive therapy	Tractotomy
Benzodiazepines		Lobectomy
Various nerve blocks		Sympathectomy
		Dorsal column stimulation
		Brain stimulation

Treatment

Treatment of phantom pain after amputation is difficult. Various treatment regimens have been, or are currently, in use. A survey of the literature in 1980 identified 68 different methods, of which 50 were still in use.[79] Clear evidence-based guidelines for the treatment of phantom pain can not be given, as most studies suffer from major methodological errors, such as small sample size, no or insufficient blinding and randomization, and short follow-up periods.[6] Until more reliable data become available, guidelines are probably the best approach. The situation is similar for other neuropathic pain states, for example, post-herpetic neuralgia and diabetic neuropathy. Treatment of phantom pain can be classified as medical, non-medical and surgical. Medical treatment is the most effective. In general, treatment should be based on non-invasive techniques as surgical procedures carry a risk of further deafferentiation resulting in even more pain. Table 3 lists treatments used for phantom pain.

Medical treatment

Numerous medical interventions have been proposed over the years but tricyclic antidepressants (TCA) and sodium channel blockers are currently considered to be the drug treatments of choice for neuropathic pain.[86]

A large number of randomized, controlled clinical trials have shown a beneficial effect of TCA in different neuropathic pain conditions and, recently, amitriptyline was shown to relieve nerve injury pain.[40] No controlled trials have been performed in phantom limb pain but TCAs are generally considered to be effective. Selective serotonin reuptake inhibitors (SSRI) are probably less effective in neuropathic pain. The TCA drug doxepin was reported to be effective in the treatment of phantom pain.[33] Others have reported a beneficial effect of the benzodiazepine clonazepam.[7] However, there is a general clinical impression that benzodiazepines do not produce substantial pain relief.

Carbamazepine, an anticonvulsant drug which is effective in neuropathic pain,[86] is a non-specific sodium channel blocker. Case reports have suggested that it is effective in phantom pain.[21,68] Novel anticonvulsants such as lamotrigine and gabapentin may also prove to effective in phantom pain.

Lidocaine and its oral congener mexiletine are used in different neuropathic pain conditions.[52] I.v. lidocaine was reported to be effective in neuropathic pain.[8] In an open-label study, mexiletine produced pain relief in 18 of 31 patients with phantom pain.[12]

Calcitonin may be effective in phantom pain. In a double-blind, crossover study, Jaeger and Maier demonstrated that i.v. calcitonin was effective in phantom pain when used in the early post-operative period.[35]

The effect of NMDA receptor antagonists have been examined in different neuropathic pain conditions, including phantom pain.[58,61,87] In a double-blind, placebo-controlled study, i.v. ketamine reduced pain, hyperalgesia and 'wind-up' like pain in 11 amputees with stump and phantom pain.[58] Memantine is another NMDA receptor antagonist available for oral use. In a recent double-blind, crossover trial, patients with pain following amputation (n=15) or nerve injury (n=4) were randomized to receive memantine or placebo in a 5-week treatment period. A washout period of 4 weeks was followed by another 5-week treatment period. Memantine, at a daily dose up to 20 mg, failed to have an effect on spontaneous pain, allodynia and hyperalgesia.[61]

Opioids were previously thought to be ineffective in neuropathic pain. Controlled studies are still lacking. However, presently, many feel that some patients can benefit from opioids with a limited risk of drug dependence.[6,14] The analgesic effect of oral and intrathecal opioids in phantom pain has been described by several authors.[34,65,90] Tramadol is an analgesic with both monoaminergic and opioid activity and it may prove to be an alternative to strong opioids as tolerance and dependence during long-term treatment with tramadol appears to be uncommon. NSAIDs and paracetamol are considered to be ineffective in phantom pain by most practitioners.

A large number of other treatments, for example, beta-blockers,[1] topical application of capsaicin,[74] various anaesthetic blocks[50,94] have been claimed to be effective in phantom pain but none of them have proven to be effective in well-controlled trials.

Non-medical treatment

Medical treatment can be combined with various non-invasive techniques such as transcutaneous electrical nerve stimulation (TENS), vibration therapy, acupuncture, hypnosis, biofeedback, and electroconvulsive therapy.[43,51,73,84] Despite the widespread use of some of these techniques clear evidence of effect is limited[22] (for review[28]). In a placebo-controlled, crossover design, Katz and Melzack found that TENS, applied to the outer ear, reduced phantom pain.[43] Lundeberg and colleagues found a similar effect of vibration therapy.[51]

Electrical stimulation of the spinal cord, deep brain structures, and motor cortex may relieve chronic neuropathic pain, including phantom pain. However, the effect of treatment often decreases with time.[47 55] (for review[85])

Surgical treatment

Surgical treatment for phantom pain has been attempted for decades but the results have generally been unfavourable. Stump revision or neurectomy may be effective if there is local specific pathology at the stump but, in properly healed stumps, there is almost never an indication for proximal extension of the amputation because of pain. Dorsal root entry zone (DREZ) lesions were primarily introduced for the treatment of painful brachial plexus avulsions but the treatment has also been used in phantom pain.[76] It is believed to have a limited effect. Other neurosurgical techniques, for example, cordotomy, thalamotomy, sympathectomy may provide short-term pain relief but pain often reappears. These treatments have been most abandoned today.

Prevention

The idea of a pre-emptive analgesic effect in phantom pain was initiated by observations that phantom pain in some cases seemed to be similar to pain experienced before the amputation[5 29 56] and that the presence of severe pain before amputation was associated with a higher risk of post-amputation phantom pain.[3 38 75] It was hypothesized that pre-amputation pain created an imprint in the memorizing structures of the central nervous system and that such an imprint could be responsible for persistent pain after amputation. Therefore, Bach and colleagues carried out a controlled study to examine if pre-operative epidurals could reduce the risk of phantom pain. They randomized 25 patients undergoing amputation of the lower limb by means of their year of birth to receive either epidural morphine, epidural bupivacaine or both in combination for 3 days before amputation (n=11) or conventional analgesia (n=14). All patients received epidural or spinal analgesia for amputation and 'post-operatively' their pain was treated with conventional analgesics. Patients were questionned about phantom pain after 1 week, and 6 and 12 months. Pain was categorized as either present or not present and, apparently, interviewers were not blinded to the treatment. Six patients died during the follow-up period. The incidence of phantom pain was reduced 6 months after amputation but not after 1 week or after 12 months in the epidural treatment group as compared with the control group.[4] Subsequent clinical trials have confirmed these results.

Jahangiri and colleagues prospectively followed 24 patients undergoing limb amputation. In a non-randomized design, patients received either an epidural infusion of bupivacaine, diamorphine and clonidine from 24 to 48 h pre-operatively and for at least 3 days after surgery (n=13) or on demand opioids (n=11). Amputation was carried out under general anaesthesia. The presence of phantom pain was graded on a scale of 1–10 and pain was considered significant when the score was $\geqslant$3. During follow-up, two patients died. The incidence of phantom pain was significantly lower in the epidural group after 1 week, and 6 and 12 months.[36]

In a letter, Schug and colleagues presented data from a non-randomized trial. Methods of blinding and pain assessment were not described. Twenty-three patients were divided into three groups. One group received an epidural infusion of bupivacaine and fentanyl for 24 h before amputation and continued for at least 48 h after surgery (n=8). Another group (n=7) had epidural anaesthesia for the amputation and 'post-operatively' pain was treated with epidural infusion of bupivacaine and fentanyl. The third group (n=8) received surgery under general anaesthesia and systemic analgesia for pain. After 1 yr, the incidence of phantom pain was significantly lower in the patients who had received pre-, intra- and post-operative epidural analgesia.[78]

Katsuly-Liapis and colleagues reported in abstract form 45 patients who were randomized into three groups to receive: (1) epidural analgesia with bupivacaine and morphine for 3 days before amputation and continued for 3 days after surgery (n=15), (2) epidural analgesia post-operatively (n=12) or (3) systemic analgesia with opioids and NSAID (n=18). After 6 months, the incidence of phantom pain was significantly lower in the patients who had epidural analgesia before, during, and after amputation compared with the other two groups. No details with respect to randomization, blinding, or pain assessment were presented.[41]

In a blinded and placebo-controlled trial, Nikolajsen and colleagues randomly assigned 60 patients into two groups. All patients had an epidural catheter on the day before the amputation. The epidural treatment group (n=29) received a pre-operative infusion of epidural bupivacaine and morphine for a median time of 18 h and the infusion was continued during the amputation. The control group (n=31) received equivalent amounts of epidural saline and systemic opioids. Both groups had general anaesthesia for the amputation and all received epidural bupivacaine and morphine for post-operative pain management. Phantom pain was assessed after one week, and 3, 6 and 12 months by a visual analogue scale (VAS). Blinding was ensured by the use of two independent investigators. One investigator was responsible for inclusion of patients and for post-operative pain assessment and the other for randomization and pre- and intra-operative pain treatment. The number of patients was reduced to 28 after 1 yr, mainly because of death. After 1 week, 52% of patients in the epidural treatment group and 56% of patients in the control group had phantom pain. Incidence and intensity of phantom pain were also similar in the two groups at the later post-operative interviews.[60] So, according to this study, it is not possible to prevent phantom pain by a epidural block of short duration.

Others have examined the effect of a post-operative perineural analgesia on the prevention of phantom pain. Fisher and Meller (1991) introduced a catheter into the nerve sheath at the time of amputation and infused bupivacaine for 72 h post-operatively.[23] Similar methods were used by Elizaga and colleagues[20] and Pinzur and coworkers[70] but only the study by Fisher and Meller found an effect of treatment.[23]

Conclusion

It may not be possible to prevent phantom pain by pre-emptive approaches. A further understanding of the mechanisms underlying pain in amputees may lead to new and rational treatments. In future, perhaps we will see the development of new drugs with fewer side effects compare with drugs we use today.

References

1 Ahmed S. Phantom limb pain and propranolol. *BMJ* 1979; **1**: 415

2 Amir R, Devor M. Ongoing activity in neuroma afferents bearing retrograde sprouts. *Brain Res* 1993; **630**: 283–8

3 Appenzeller O, Bicknell JM. Effects of nervous system lesions on phantom experience in amputees. *Neurology* 1969; **19**: 141–6

4 Bach S, Noreng MF,Tjéllden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301

5 Bailey AA, Moersch FP. Phantom limb. *Can Med Assoc* 1941; **45**: 37–42

6 Baron R, Wasner G, Lindner V. Optimal treatment of phantom limb pain in the elderly. *Drugs Aging* 1998; **12**: 361–76

7 Bartusch SL, Sanders J, Dálessio JG, Jernigan JR. Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; **12**: 59–62

8 Boas RA, Covino BG, Shahnarian A. Analgesic responses to i.v. lidocaine. *Br J Anaesth* 1982; **54**: 501–5

9 Carlen PL, Wall PH, Nadvorna H, Steinbach T. Phantom limbs and related phenomena in recent traumatic amputations. *Neurology* 1978; **28**: 211–7

10 Chabal C, Jacobson L, Russell L, Burchiel KJ. Pain responses to perineuromal injection of normal saline gallamine, and lidocaine in humans. *Pain* 1989; **36**: 321–5

11 Chabal C, Jacobson L, Russell L, Burchiel KJ. Pain responses to perineuromal injection of normal saline, epinephrine, and lidocaine in humans. *Pain* 1992; **49**: 9–12

12 Davis RW. Successful treatment for phantom pain. *Orthopedics* 1993; **16**: 691–5

13 Davis KD, Kiss ZHT, Luo L, Tasker RR, Lozano AM, Dostrovsky JO. Phantom sensations generated by thalamic microstimulation. *Nature* 1998; **391**: 385–7

14 Dellemijn P. Are opioids effective in relieving neuropathic pain? *Pain* 1999; **80**: 453–62

15 Devor M, Govrin-Lippman R, Angelides K. Na$^+$ channels immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci* 1993; **135**: 1976–92

16 Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurones by sympathetic activation in nerve-injured rats. *J Neurophysiol* 1994; **71**: 38–47

17 Devor M, Seltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 129–64

18 Dostrovsky JO. Immediate and long-term plasticity in human somatosensory thalamus and its involvement in phantom limbs. *Pain Suppl* 1999; **6**: 37–43

19 Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 165–81

20 Elizaga AM, Smith DG, Sharar SR, Edwards T, Hansen ST. Continuous regional analgesia by intraneural block: effect on postoperative opioid requirements and phantom limb pain following amputation. *J Rehab Res Dev* 1994; **31**: 179–87

21 Elliott F, Little A, Milbrandt W. Carbamazepine for phantom limb phenomena. *N Engl J Med* 1976; **295**: 678

22 Ezzo J, Berman B, Hadhazy VA, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? *Pain* 2000; **86**: 217–25

23 Fisher A, Meller Y. Continuous postoperative regional analgesia by nerve sheath block for amputation surgery—a pilot study. *Anesth Analg* 1991; **72**: 300–3

24 Florence SL, Kaas JH. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J Neurosci* 1995; **15**: 8083–95

25 Flor H, Elbert T, Muhlnickel, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Exp Brain Res* 1998; **119**: 205–12

26 Furukawa T. Charles Bell's description of the phantom phenomenon in 1830. *Neurology* 1990; **40**: 1830

27 Hanowell ST, Kennedy SF. Phantom tongue pain and causalgia: case presentation and treatment. *Anesth Analg* 1979; **58**: 436–8

28 Hansson P, Lundeberg T. Transcutaneous electrical nerve stimulation, vibration and acupuncture as pain relieving measures. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 1341–51

29 Henderson WR, Smyth GE. Phantom limbs. *J Neurol Neurosurg Psych* 1948; **11**: 88–112

30 Herrmann LG, Gibbs EW. Phantom limb pain. Its relation to the treatment of large nerves at time of amputation. *Am J Surg* 1945; **67**: 168–80

31 Hill A, Niven CA, Knussen C: *Pain* memories in phantom limbs: a case study. *Pain* 1996, **66**: 381–4

32 Houghton AD, Nicholls G, Houghton AL, Saadah E, McColl L. Phantom Pain: natural history and association with rehabilitation. *Ann R Coll Surg Engl* 1994; **76**: 22–5

33 Iacono RP, Sandyk R, Baumford CR, Awerbuch G, Malone JM. Post-amputation phantom pain and autonomous stump movements responsive to doxepin. *Function Neurol* 1987; **2**: 343–8

34 Jacobsen L, Chabal C, Brody MC. A comparison of the effects of intrathecal fentanyl and lidocaine on established postamputation stump pain. *Pain* 1990; **40**: 137–41

35 Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. *Pain* 1992; **48**: 21–27

36 Jahangiri M, Bradley JWP, Jayatunga AP, Dark CH. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. *Ann R Coll Surg Engl* 1994; **76**: 324–6

37 Jensen TS, Krebs B, Nielsen J, Rasmussen P. Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation. *Pain* 1983; **17**: 243–56

38 Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. *Pain* 1985; **21**: 267–78

39 Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. *Neurosci Lett* 1992; **138**: 225–8

40 Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 1995; **64**: 293–302

41 Katsuly-Liapis I, Georgakis P, Tierry C. Preemptive extradural analgesia reduces the incidence of phantom pain in lower limb amputees. Abstract. *Br J Anaesth* 1996; **76**: 125

42 Katz J, Melzack R. Pain 'memories' in phantom limbs: review and clinical observations. *Pain* 1990; **43**: 319–36

43 Katz J. Melzack R. Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain. *J Pain Symptom Manage* 1991; **6**: 73–83

44 Katz J. Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psych* 1992; **50**: 811–21

45 Keil G. Sogenannte erstbeschreibung des phantomschmerzes von Ambroise Paré. *Fortschr Med* 1990; **108**: 62–6

46 Kooijman CM, Dijkstra PU, Geertzen JHB, Elzinga A, Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. *Pain* 2000; **87**: 33–41

47 Krainick J-U, Thoden U, Riechert T. Pain reduction in amputees by long-term spinal cord stimulation. *J Neurosurg* 1980; **52**: 346–50

48 Krane EJ, Heller LB. The prevalence of phantom sensation and pain in pediatric amputees. *J Pain Sympt Manage* 1995; **10**: 21–9

49 Krøner K, Krebs B, Skov J, Jørgensen HS. Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. *Pain* 1989; **36**: 327–34

50 Lierz P, Schroegendorfer K, Choi S, Felleiter P, Kress HG. Continous blockade of both brachial plexus with ropivacaine in phantom pain: a case report. *Pain* 1998; **78**: 135–7

51 Lundeberg T. Relief of pain from nine phantom limbs by peripheral stimulation. *J Neurol* 1985; **232**: 79–82

52 Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain* 2000; **87**: 7–17

53 Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci USA* 1999: **96**: 7744–51

54 Montoya P, Larbig W, Grulke N, Flor H, Taub E, Birbaumer N. The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees. *Pain* 1997; **72**: 87–93

55 Mundinger F, Salomáo JF. Deep brain stimulation in mesencephalic lemniscus medialis for chronic pain. *Acta Neurochir* 1980; **30**: 245–58

56 Nathan PW. Pain traces left in the central nervous system. In: Keele CA, Smith R, eds. *The Assessment of Pain in Man and Animals.* Edinburgh: E & S Livingstone, 1962; 129–34

57 Nathanson M. Phantom limbs as reported by S. Weir Mitchell. *Neurology* 1988; **38**: 504–5

58 Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996; **67**: 69–77

59 Nikolajsen L, Ilkjær S, Krøner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997; **72**: 393–405

60 Nikolajsen L, Ilkjær S, Krøner K, Christensen JH, Jensen TS. Randomized trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997; **350**: 1353–7

61 Nikolajsen L, Gottrup H, Kristensen AGD, Jensen TS. Memantine (a *N*-methyl D-aspartate receptor antagonist) in the treatment of neuropathic pain following amputation or surgery—a randomized, double-blind, cross-over study. *Anesth Analg* 2000; **91**: 960–6

62 Nikolajsen L, Ilkjær S, Jensen TS. Relationship between mechanical sensitivity and postamputation pain: a prospective study. *Eur J Pain* 2000; **4**: 1–8

63 Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M, Sangameswaran L, Gogas KR, Eglen RM, Hunter JC. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic pain conditions. *J Neurosci* 1998; **18**: 2174–87

64 Nyström B, Hagbarth KE. Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci Lett* 1981; **27**: 211–6

65 Omote K, Ohmori H, Kawamata M, Matsumoto M, Namiki A. Intrathecal buprenorphine in the treatment of phantom limb pain. *Anesth Analg* 1995; **80**: 1030–2

66 Ovesen P, Krøner K, Ørnsholdt J, Bach K. Phantom-related phenomena after rectal amputation: prevalence and clinical characteristics. *Pain* 1991; **44**: 289–91

67 Parkes CM. Factors determining the persistence of phantom pain in the amputee. *J Psychosom Res* 1973; **17**: 97–108

68 Patterson JF 1988 Carbamazepine in the treatment of phantom limb pain. *South Med J* 1988; **81**: 1101–2

69 Pezzin LE, Dillingham TR, Mackenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. *Arch Phys Med Rehabil* 2000; **81**: 292–300

70 Pinzur MS, Garla PGN, Pluth T, Vrbos L. Continous postoperative infusion of a regional anaesthetic after an amputation of the lower extremity. *J Bone Joint Surg* 1996; **78**: 1501–5

71 Pohjolainen T. A clinical evaluation of stumps in lower limb amputees. *Prosthet Orthot Int* 1991; **15**: 178–84

72 Rajbhandari SM, Jarett JA, Griffiths PD, Ward JD. Diabetic neuropathic pain in a leg amputated 44 years previously. *Pain* 1999, **83**: 627–9

73 Rasmussen KG, Rummans. Electroconvulsive therapy for phantom limb pain. *Pain* 2000; **85**: 297–9

74 Rayner HC, Atkins RC, Westerman RA. Relief of local stump pain by capsaicin cream. *Lancet* 1989; **2**: 1276–7

75 Riddoch G. Phantom limbs and body shape. *Brain* 1941; **64**: 197–222

76 Saris SC, Iacono RP, Nashold BS Jr. Successful treatment of phantom pain with dorsal root entry zone coagulation. *Appl Neurophysiol* 1988; **51**: 188–97

77 Schott GD. Pain and its absence in an unfortunate family of amputees. *Pain* 1986; **25**: 229–31

78 Schug SA, Burrell R, Payne J, Tester P. Pre-emptive epidural analgesia may prevent phantom limb pain. *Region Anesth* 1995; **20**: 256

79 Sherman RA, Sherman CJ, Gall NG. A survey of current phantom limb treatment in the United States. *Pain* 1980; **8**: 85–99

80 Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey. *Am J Phys Med* 1983; **62**: 227–38

81 Sherman RA, Sherman CJ. A comparison of phantom sensations among amputees whose amputations were of civilian and military origins. *Pain* 1985; **21**: 91–7

82 Sherman RA, Glenda GM. Concurrent variation of burning phantom limb and stump pain with near surface blood flow in the stump. *Orthopedics* 1987; **10**: 1395–402

83 Sherman RA, Vernice GD, Evans CB. Temporal relationship between changes in phantom limb pain intensity and chances in surface electromyogram of the residual limb. *J Int Psychophysiol* 1992; **13**: 71–7

84 Siegel EF. Control of phantom limb pain by hypnosis. *Am J Clin Hypnosis* 1979; **21**: 285–6

85 Simpson BA. Spinal cord and brain stimulation. In: Wall PD, Melzack R, eds. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 1353–81

86 Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; **83**: 389–400

87 Stannard C F, Porter G E. Ketamine hydrochloride in the treatment of phantom limb pain. *Pain* 1993; **54**: 227–230

88 Tessler MJ, Kleiman SJ. Spinal anaesthesia for patients with previous lower limb amputations. *Anaesthesia* 1994; **49**: 439–41

89 Torebjork E, Wahren L, Wallin G, Koltzenburg M. Noradrenaline-evoked pain in neuralgia. *Pain* 1995; **63**: 11–20

90 Urban BJ, France RD, Steinberger EK, Scoot DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb. *Pain* 1986; **24**: 191–6

91 Wall PD, Gutnick M. Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. *Exp Neurol* 1974; **43**: 580–93

92 Wall R, Novotny-Joseph P, Macnamara TE. Does preamputation pain influence phantom limb pain in cancer patients? *South Med J* 1985; **78**: 34–6

93 Wartan SW, Hamann W, Wedley JR, McColl I. Phantom pain and sensation among British veteran amputees. *Br J Anaesth* 1997; **78**: 652–9

94 Wassef MR. Phantom pain with probable reflex sympathetic dystrophy. Efficacy of fentanyl infiltration of the stellate ganglion. *Region Anesth* 1997; **22**: 287–90

95 Waxman SG. The molecular pathophysiology of pain: abnormal expession of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. *Pain Suppl* 1999; **6**: 133–40

96 Weiss SA, Lindell B. Phantom limb pain and etiology of amputation in unilateral lower extremity amputees. *J Pain Symptom Manage* 1996; **11**: 3–17

97 Weiss T, Miltner WH, Adler T, Bruckner L, Taub E. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. *Neurosci Lett* 1999; **272**: 131–4

98 Whitaker HA. A historical note on phantom limb. *Neurology* 1979; **29**: 273

99 Wilkins KL, McGrath PJ, Finley GA, Katz J. Phantom limb sensations and phantom limb pain in child and adolescent amputees. *Pain* 1998; **78**: 7–12

100 Woolf CJ, Shortland P, Coggeshaal RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992; **355**: 75–8

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Trigeminal neuralgia—pathophysiology, diagnosis and current treatment

T. J. Nurmikko[1]* and P. R. Eldridge[2]

[1]Pain Research Institute, Department of Neurological Science, University of Liverpool, Liverpool, UK.
[2]The Walton Centre for Neurology and Neurosurgery NHS Trust, Liverpool, UK
**Corresponding author*

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Historical aspects

The first known description of trigeminal neuralgia (TGN), or a similar condition, was written in the second century AD by Aretaeus of Cappadocia, a contemporary of Galen. Also known for his descriptions of migraine, he makes reference to a pain in which 'spasm and distortion of the countenance take place'.[113] Jujani, an 11th century Arab physician, mentions unilateral facial pain causing spasms and anxiety in his writings. Interestingly, he suggests that the cause of the pain is 'the proximity of the artery to the nerve'.[4] The first full account of TGN was published in 1773 when John Fothergill presented a paper to the Medical Society of London. He described the typical features of the condition in detail, including paroxysms of unilateral facial pain, evoked by eating or speaking or touch, starting and ending abruptly, and associated with anxiety.[113] Some time earlier, Nicolaus André had used the term 'tic douloureux' to describe what he thought was a new clinical entity. However, it has been suggested, that no more than two of the patients he described in fact had TGN.[4]

Sporadic observations later in the 18th and 19th century by Pujol, Chapman and Tiffany helped to complete the clinical picture and differentiate TGN from common facial pain conditions such as toothache. In the early 20th century, Oppenheim alluded to an association between multiple sclerosis (MS) and TGN and Patrick commented on its familial incidence.[39]

A wide range of treatments was in use by the beginning of the last century. Modern neurosurgical treatment can be traced back to 1925 when the concept of vascular compression was introduced.[29] However, it took over half a century before microvascular decompression (MVD) gained wide-spread acceptance as a treatment method. Gardner and Miklos promoted the theory and modified the technique further in the 1950s and 1960s.[41] It was not until the large case series published in 1970s by Jannetta[58] that a major shift in neurosurgical practice began to appear. Neuroablative procedures kept evolving throughout the century, with attempts to balance the adverse effects of neural injury with sufficient pain control. Radiosurgery is the latest innovation in this process.

Pharmacotherapy had little success in this condition until Bergouignan's discovery in 1942 that phenytoin was effective in preventing pain paroxysms.[12] Soon, following the introduction of carbamazepine for treatment of epilepsy, controlled trials were published showing its superiority over placebo in TGN. Since then, anticonvulsants have remained the mainstay of pharmacological treatment, though controlled trials have been surprisingly rare.

Definition of TGN

Both the International Association for the Study of Pain (IASP) and International Headache Society (IHS) have suggested their own diagnostic criteria for TGN.[91] [143] These are remarkably similar and highlight the sudden, explosive nature of the pain (Table 1). In further descriptions of the condition, both classifications allude to vascular compression, MS and tumours as known aetiological causes. The IASP classification makes a distinction between TGN (including MS) and secondary neuralgias (caused by structural lesions and injuries, but not including MS), while IHS separates idiopathic TGN from the 'symptomatic form' depending on the presence of a structural lesion; it is not quite clear if vascular compression qualifies as such. Neither approach includes reference to variant forms of TGN, which satisfy the diagnostic criteria but display additional features as well.

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Table 1 Definition of TGN provided by the International Association for the Study of Pain, IASP[91] and International Headache Society, IHS[143]

IASP definition	IHS definition
Sudden, usually unilateral, severe brief stabbing recurrent pains in the distribution of one or more branches of the Vth cranial nerve	Painful unilateral affliction of the face, characterized by brief electric shock like pain limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking, and brushing the teeth, but may also occur spontaneously. The pain is abrupt in onset and termination and may remit for varying periods

Diagnosis

Several authors have used a slightly different approach by classifying TGN patients into subgroups depending on how 'pure' the pain is.[16 20 81 99 122 140] We agree with this viewpoint, because our own experience reflects the general conclusion that the outcome is dependent on the nature of the pain. We have also frequently witnessed, in our tertiary referral clinic, both over- and under-diagnosing of TGN, which seems to reflect difficulties in interpreting the painful symptoms in the context of an unnecessarily restrictive 'official' definition.

Our own classification and diagnostic criteria are presented in Table 2. We use it as guidance, rather than a fixed set of rules. While arbitrary, it has worked well in our hands and greatly helped communication between various specialists. It is obvious that, in some cases, pain slowly evolves from one category to another. A typical form of TGN may, in prolonged cases, develop atypical signs, as observed by Burchiel.[20] By contrast, many cases of TGN start with pain lacking the typical characteristics of TGN, but respond well to carbamazepine, and later developing all the hallmark signs of TGN ('pre-TGN').[38]

Trigeminal neuropathy, whether painful or non-painful, is associated with a structural lesion or systemic disease. It may be seen following direct trauma to the nerve (e.g. supra- and infra-orbital neuralgias following facial fractures); we also classify dysaesthesiae and anaesthesia dolorosa following neuroablative procedures as trigeminal neuropathy. On occasion, it can be seen caused by severe arterial compression, usually from an ectatic basilar artery. The pain description in this condition is different from that in TGN and more akin to that in painful peripheral neuropathy. Pain is usually constant and associated with allodynia and sensory loss. Central nervous system lesions, even if they predominantly involve the trigeminal pathways and very occasionally mimic TGN, are not classified as either trigeminal neuropathy or TGN, but fall under the heading of central pain.

TGN remains a clinical diagnosis dependent on a history of sudden shooting or stabbing pain, coming as solitary sensations or paroxysms and separated by pain-free intervals. Optimally, it is the patient who volunteers this description. However, many patients with facial pain have considerable difficulty in finding precise expressions to convey the characteristics of their symptoms. In such a case, the interviewer may suggest descriptive words with as little prompting as possible. Some patients identify the type of pain if an acoustic equivalent of the pain is provided, for example, by the interviewer sharply clapping his hands. Although the McGill Pain Questionnaire has been shown to be useful in differentiating a group of TGN patients from those with other facial pains,[90] our observations suggest that, in individuals, taking a careful history is unsurpassed in providing the most reliable elements for the diagnosis.

Patients with atypical TGN also give the history of stabbing or shooting pains. Unlike in typical TGN, they relate a history of other kinds of pain as well. Many have constant or near constant discomfort on the same side of the face. We are not aware of studies focussing on atypical forms. Many patients we see are those with recurrent TGN with a history of previous neuroablative procedures. It remains a possibility that compression of the nerve, when protracted, can lead to intrinsic changes in the nerve and modify the clinical picture.[20]

In addition, non-verbal behaviour may be very helpful in aiding the diagnosis. Patients with severe TGN either wince or interrupt their speech as a result of a tic. Many show major aversion to anyone or anything touching the face. This may, in fact, influence the clinical examination. By contrast, patients with other types of facial pain, including trigeminal neuropathy, usually seem not to be bothered by the their hand or the examiner's hand touching their face.

Differential diagnosis

The list of differential diagnoses is long and includes a number of pathological conditions affecting the sinuses, teeth, temporomandibular joints, eyes, nose, and the neck. Most of these are easily ruled out after the interview and brief clinical examination. However, a few conditions remain that bear considerable similarity to TGN and are listed in Table 3.

Other cranial neuralgias (glossopharyngeal neuralgia, neuralgia of nervus intermedius, neuralgia of the superior laryngeal nerve, and occipital neuralgia) can all cause diagnostic difficulty. These neuralgias are rare and can produce pain that is identical to that of TGN. However, the location is different.

Aetiology of TGN

There are obvious problems in determining aetiological causes for a syndrome, which is formulated on the basis of

Table 2 Comparison of definitions of TGN. *Key items

	TGN (IASP and IHS definition)	**Typical TGN (Liverpool criteria)**	**Atypical TGN (Liverpool criteria)**	**Trigeminal neuropathy (Liverpool criteria)**
Site*	Unilateral	Unilateral	Unilateral	Uni- or bilateral
Quality of pain*	Sharp, stabbing, burning, superficial	Sharp, shooting, stabbing, lingering aftersensations	Sharp shooting, stabbing, lingering aftersensations, burning, smarting	Dull or sharp, smarting, steady pain with shooting sensations superimposed
Duration of pain*	Brief	A few seconds at most	Several seconds	Any duration, usually hours
Duration of paroxysms	Seconds to 2 minutes	Seconds to minutes	Seconds to minutes	Continuous with pain-free spells
Refractory period	Yes	Yes	Yes	No
Continous pain	No	No	Yes, not severe	Dominant feature
Allodynia*	Limited trigger zones	Small trigger zones	Small trigger zones	Large allodynic areas
Associated features	Slight flush	Vasodilatation, swelling seen with severe pain	Vasodilatation, swelling seen with severe pain	Variable vasodilatation and swelling, may be constantly present
Radiation	None outside affected division	None outside affected division	None outside affected division	May extend outside trigeminal territory
Provoking factors*	Eating, talking, washing face, brushing teeth, smoking	Touching, speaking, eating, drinking, cold, not heat, movement	Touching, speaking, eating, drinking, cold, occasionally heat, movement	Same as atypical TGN
Variability of pain	Stereotyped	Some variation	Definite variation	Definite variation
Sensory loss*	None	Not detectable with bedside tests QST may be abnormal	May be detectable with bedside tests QST usually abnormal	Prominent, easily detected with bedside tests, confirmed by QST
Pain behaviour	Not discussed	Aversion to touch guarded speech	Aversion to touch guarded speech	Tolerates touching speech not affected
Course of pain*	Spontaneous remissions	Early remissions pre-TGN	Early remissions previously typical TGN	No remission; slow progression

subjective pain rather than hard signs or laboratory abnormalities. However, in the last three decades, evidence has been mounting that in a large proportion of cases, compression of the trigeminal nerve root at or near the dorsal root entry zone by a blood vessel is a major causative or contributing factor. There are several lines of evidence that support this view. First, novel imaging methods (MRI) and observations during posterior fossa surgery for TGN have consistently shown a blood vessel in contact with the nerve root.[13 88] Second, elimination of the compression leads to long-term pain relief in most patients.[10] Third, intra-operative recordings show immediate improvement in nerve conduction following decompression, fitting with the general experience that patients tend to wake up from the operation pain-free.[76] Fourth, sensory functions recover as well following decompression (though this recovery is slower than that in nerve conduction).[92]

Some authors have questioned the significance of the vascular compression by pointing out that it is not unusual to see blood vessels in the vicinity of or touching the nerve during a routine autopsy in patients with no history of TGN.[2 3] However, as underlined by many others, the critical abnormality is vascular contact at the dorsal root entry zone, rather than more distally; such is seen in 3–12% of trigeminal nerves at autopsy.[48 50] The way the autopsy is carried out may be relevant. Hamlyn and colleagues have suggested that their method of positioning the cadaver to mimic the positioning during the actual operation and perfusing the arteries and veins at physiological pressures to prevent them from collapsing leads to a more reliable assessment of any significant neurovascular compression.[48] They found a blood vessel contact in 13% of the cadavers, but without concomitant grooving of any of the affected nerves. A contact at the level of the dorsal root entry zone by an artery was found in 3% and by a vein by 6% of their material.[48]

Of other known aetiological factors, the association of MS with TGN is well established.[60 108 115] MS is seen in 2–4% of patients with TGN.[51 60 61 115] Conversely, TGN is diagnosed in 1–5% of patients with MS.[27 53 94 115 123] In a small proportion of patients with MS, TGN is the first manifestation of the disease. These patients are younger than the TGN population as a whole and their neuralgia is more frequently bilateral. A latent demyelinating disease

Table 3 Differential diagnosis of TGN. *SUNCT, Short-lasting, unilateral, neuralgiform headcahe with conjunctival injection and tearing; **CPH, chronic paroxysmal hemicrania. Sources: Goadsby and Lipton,[43] Merskey and Bogduk,[91] and Zakrzewska[141]

Condition	Location of pain	Duration of pain or attack	Shooting pain or paroxysms	Autonomic symptoms	Pain relief with carbamazepine	Comments
Cluster headache	Retrobulbar, cheek, chin	20 min to hours	Only superimposed on deep dull pain	Prominent	Slight	Triptans help Alcohol provokes
SUNCT*	Forehead, retrobulbar	5 s to several minutes	Yes	Prominent	None	Almost exclusively in women; rare
CPH**	Forehead, retrobulbar	2–45 min	No	Prominent	None	Responsive to indomethacin
Cracked tooth syndrome	Upper jaw lower jaw	Seconds	Yes	None	None	Provoked on biting and chewing
Jabs and jolts syndrome	Anywhere in the head	Seconds	Yes	None	Good	No precipitating factors
Post-herpetic neuralgia	Forehead, eye, cheek (rarely)	Continuous	Superimposed background pain	Variable, mild	Variable, usually modes	History of shingles Tactile allodynia, Sensory impairment
Giant cell arteritis	Forehead, neck, temple	Continuous	None	None	None	Jaw claudication

should be considered in young patients with TGN and appropriate diagnostic tests performed, as disease-modifying treatment for MS is emerging.[57]

Neuropathological and imaging studies suggest that the common denominator in patients with typical TGN and MS is the involvement of the trigeminal nerve entry zone in the pons.[42 60] In contrast, plaques in other parts of the brain stem or elsewhere in the CNS do not necessarily lead to development of TGN. Interestingly, there are reports of vascular compression of the trigeminal nerve in patients with MS,[16 17 89] and pain relief following decompression, though the results are less favourable than in other TGN subgroups.[16 17]

Tumours, usually posterior fossa meningiomas or neuromas, are found in 2% of patients who present with typical TGN.[26] The localization of the tumour dictates the nature of facial symptoms. Tumours affecting the peripheral branches or the Gasserian ganglion usually give rise to sensory change and constant pain, in other words, trigeminal neuropathy.[19 26] Slowly growing tumours which distend the trigeminal root rather than invade it, are usually found in TGN.[26] In Cheng's series, the average delay in diagnosis of the tumour was 6.3 yr. Half of the patients developed sensory or motor deficits later.

Pathophysiology

Although there is general agreement that none of the many existing theories fully explain all known characteristics of TGN pain[67 129] the bulk of current evidence points to the trigeminal nerve rather than the CNS as the site of generation of TGN pain.[105] More specifically, the existing evidence suggests that a slowly evolving process, whether a compression exerted on the nerve by a blood vessel or tumour or alteration of neural functions by an MS plaque at the level of the dorsal root entry zone, leads to increased excitability in some of the trigeminal afferents and subsequently to typical TGN.

Part of the controversy that surrounds the pathophysiology of TGN is based on misquotations and inaccuracies. Against popular belief, sensory impairment in TGN—albeit small—has been documented by several groups, both using quantitative sensory testing and neurophysiological methods.[18 75 100] As already mentioned, these changes normalize following successful MVD.[76 92] The trigeminal ganglion in TGN is not normal but shows unique pathological changes, such as degenerative hypermyelination and formation of microneuromata, not explained by tissue artefacts, effects of aging or occult disease.[11 62 63] The ganglion cells themselves appear mostly intact. While the exact mechanisms of how these changes have come about is not clear, it is of interest that such changes were reported in a patient with MS and TGN.[11] At the site of vascular compression of the trigeminal root, electron microscopic studies show demyelination and remyelination.[63 106]

It has been suggested[25] that lack of neurogenic inflammation in TGN is evidence against a major peripheral nervous system involvement. However, vasodilatation is known to occur in TGN and it normalizes when pain is controlled.[101]

A puzzling fact in TGN is that very different treatments yield seemingly similar results in controlling TGN pain. However, closer inspection of the long-term effects suggests that simple blocks or minimally destructive peripheral procedures lead to transient pain relief, much shorter than seen in more proximal lesions or decompression.[10 44 95 126 138] Also, following neuroablative procedures, the degree of sensory loss correlates positively with the duration of pain relief.[126] If one assumes that the dynamic pain of TGN reflects a state of hyperexcitability in the trigeminal afferents rather than a fixed anatomical aberration constantly driving the pain mediating fibres, then either permanent destruction of the relevant fibres or complete restoration of their normal functions (e.g. following decompression) will only achieve sustained pain relief. The key feature of TGN pain is its very dynamic nature, which is difficult to explain in purely anatomical terms.[105]

It is hard to dismiss as insignificant the observations made by numerous neurosurgeons during decompressive surgery that arterial compression of the root at the dorsal root entry zone is the common finding in typical TGN.[10 20 68 73 78 79 104 111 120] Similarly, in MS patients suffering from TGN, a common finding is the plaque extending into the dorsal root entry zone.[42] The dorsal root entry zone represents the junction between the peripheral and central myelins of Schwann cells and astrocytes. The central branches of the unipolar ganglion cells enter the pons through this transition zone on their course toward the brainstem and spinal nuclei. Any process at this level can potentially alter the function of the whole neurone.

The fact that TGN pain is not continuous but paroxysmal speaks against a simple compression induced generation of ectopic impulses at the level of the injury. It is more likely that the paroxysms of pain in this condition represent spontaneous discharges in select neurones whose threshold for repetitive firing has been altered. To comply with the characteristics of TGN, such firing should not only occur spontaneously but be produced frequently by innocuous tactile stimuli. Recent observations have shown that dorsal root ganglion cells possess properties that, in certain circumstances, lead to this type of firing behaviour.[6] Following spinal nerve injury, in which afferent neurones are axotomized close to their soma, most of the ectopic barrages originate in the dorsal root ganglion.[83] Intracellular recordings have indicated that this is because of an increase in subthreshold oscillations in the resting membrane potentials of a subpopulation of A-neurones reaching threshold.[83] Increased spike activity can in turn depolarize and cross-excite hyperexcitable neighbouring C-cells.[5] If sufficient neurones are recruited into this spreading cluster of discharging cells, it will lead to a nociceptive signal perceived as pain.[5 6 105] That such a signal would abruptly stop, as happens in TGN, is because of the inherent cellular self-quenching mechanisms.

As suggested by Rappaport and Devor,[105] the above cross-excitation may be at the root of the unique pain seen in TGN and offers a logical explanation for the extraordinary initial responsiveness of pain in TGN to almost any procedure aimed at the nerve. We think it is unlikely that the generator of pain is located in the central nervous system but central sensitization may well develop following prolonged barrage of nerve impulses which can explain the development of some features of atypical TGN. Equally, continuous pain in the atypical form can result from the progressive damage to the central terminals of trigeminal afferents, which become the source of continuous ectopic discharges.[20]

Investigations

No specific tests exist for the diagnosis of TGN. There is no excuse for not carrying out a clinical examination, including assessment of cranial nerve function, given the frequency of MS and tumours found in this population. Definite facial sensory loss or other cranial nerve dysfunction, if it cannot be explained by a previously known injury to the nerve, should prompt cerebral imaging.

Even in typical TGN, imaging studies may well be of use. Following the first reports of successful use of MRI in detecting vascular compression of the nerve in TGN.[8 127] Meaney and colleagues developed a specific technique to optimally image the relationship of the nerve and the blood vessels in its vicinity (magnetic resonance tomographic angiography, MRTA).[89] Essentially, by choosing specific scanning parameters to visualize blood vessels as high signal intensity structures and using thin slices, they were able to perform reconstructions around the nerve in any orientation. While arteries were easily identifiable, veins could be properly visualized only after enhancement with i.v. gadolinium (Figs 1 and 2). They validated this method in 50 patients with 55 symptomatic nerves (five patients had bilateral TGN) who underwent posterior fossa exploration. In all, 52 explorations were carried out. Neurovascular contact was confirmed at operation in all 49 cases suggested by MRTA. A further case with negative MRTA had no vascular contact. There were two false negative MRTAs and no false positives. This corresponds to a sensitivity of 100% and specificity of 96%.[89]

In a similar study of 27 patients with unilateral TGN, neurovascular compression, or its absence as shown by MRTA, was confirmed in 24 cases.[13] There were two false positives and one false negative (sensitivity of 92%, specificity of 50%). A further small study, in which visualization of nerve dislocation or actual compression only were accepted as positive findings, led to 100% specificity at the cost of low sensitivity (44%).[85]

Because to date there are no prospective studies comparing different facial pain groups and healthy controls, evaluated by radiologists blinded to the condition and side, the accuracy of MRTA in differentiating TGN form other painful trigeminal neuropathies remains uncertain. Therefore, MRTA cannot be used to diagnose TGN. Our current practice is to use MRTA to help in determining the likelihood that, at operation, a significant vessel contact will be found.

Several groups have developed electrophysiological techniques for assessment of trigeminal nerve function in the clinic.[28 56 75] There is insufficient evidence of their usefulness in either confirming or ruling out TGN. However, abnormalities in tests for eye blink and jaw reflexes strongly point to trigeminal neuropathic pain or 'atypical facial pain'.[56]

Treatment

Procedures

MVD

Since the original theory, outlined by Dandy in 1925, of vascular compression as a prominent feature of TGN, it took almost half a century until MVD was accepted as one of the major surgical methods for treating this condition. Advances in neuroanaesthesia, adoption of the operation microscope and developments in surgical techniques during this time helped to make the procedure safer and more effective.

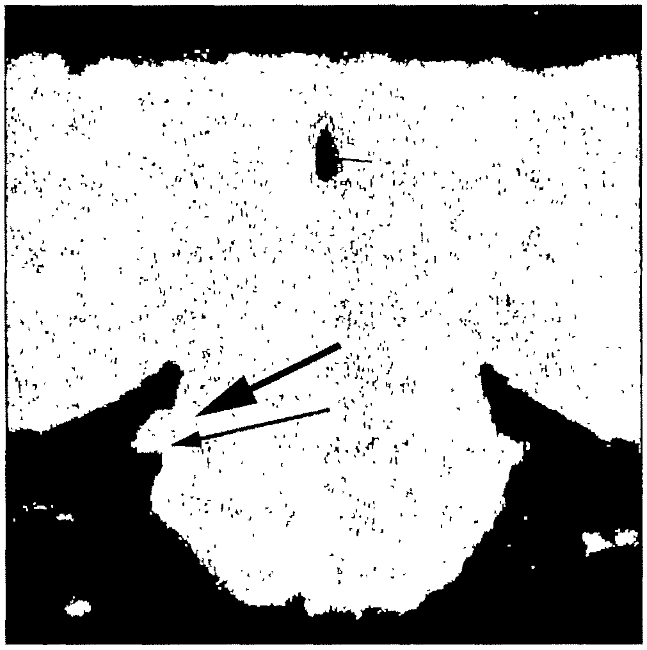

Fig 1 MRTA of a patient with right TGN. Coronal reconstruction at the level of mid-pons showing the right trigeminal nerve (thin arrow) being compressed by an artery (thick arrow).

In MVD, the target area lies at the nerve–pons junction. The posterior fossa is approached through a suboccipital craniotomy. After aspiration of the cerebrospinal fluid, the operator advances toward the nerve by gently retracting the superolateral margin of the cerebellum. The most common finding is a segment of the superior cerebellar artery compressing the nerve at the root entry zone[111] (Fig. 3). Less frequently, the anterior inferior cerebellar artery or the superior petrosal veins are the cause of the compression.[111] After the arachnoid is dissected and the vessel freed, the operator places a piece of shredded Teflon felt between the vessel and the nerve to separate them.

Monitoring of brainstem-evoked potentials during the operation (to prevent post-operative hearing loss) frequently shows temporary changes, because of traction on the eighth cranial nerve. These usually disappear if the retractor is temporarily relaxed. Most authors recommend partial section of the root if no vascular compression is found or the artery cannot be mobilized. Adams has recommended deliberate bruising of the nerve in addition to decompression,[3] but we have not found any evidence that such a manoeuvre improves the outcome.

There is no age limit for the procedure as long as the patient is fit for general anaesthesia. In our recent retrospective study in patients over 70 yr of age, pain relief and complications were no different from those seen in a group of patients under the age of 50.[59] There are anecdotal reports of MVD carried out in children less than 18[110 114] with similar results. Interestingly, venous compression appears much more common in this age group than in adults.

Several published series suggest a high level of initial success with MVD, most patients (87–98%) experiencing

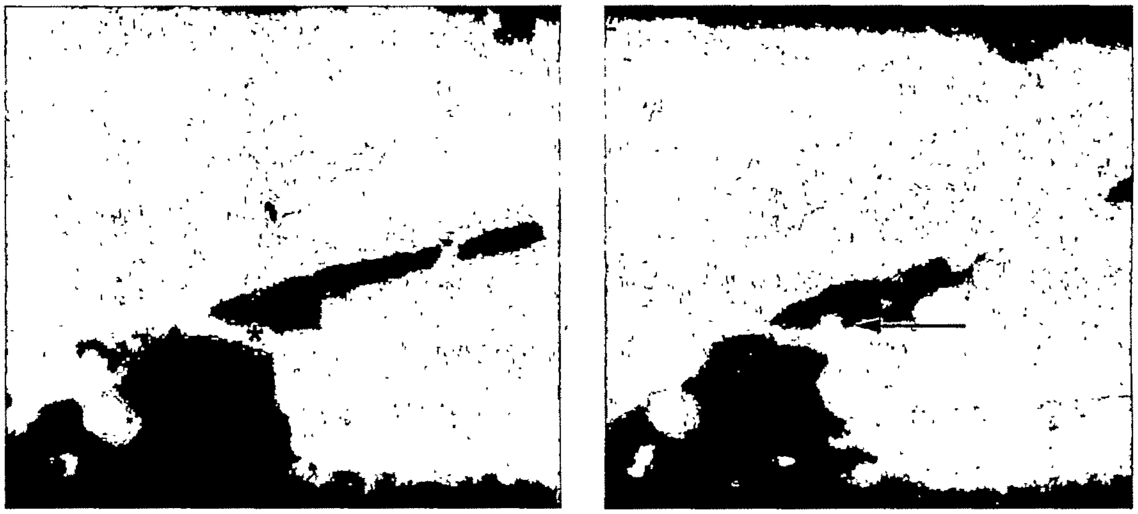

Fig 2 MRTA, sagittal reconstruction, showing the trigeminal nerve (star) and the artery compressing it from above (arrow). Same patient as in Figure 1.

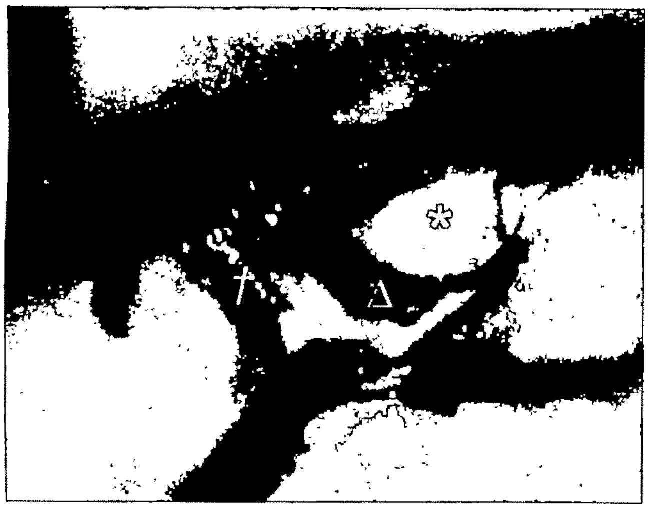

Fig 3 Microscopic view of the trigeminal nerve (star) showing an arterial loop (triangle) compressing it. A vein (cross) is seen in close proximity to the nerve as well.

immediate pain relief.[10 21 68 73 78 104 120] Those series that present the proportion of patients with unrelieved or recurrent pain using Kaplan—Meier plots, show relatively similar results.[10 21 104] At 1–2 yr the incidence of complete pain relief is 75–80%. After 8–10 yr, this proportion has been reduced to 58–64%, with a further 4–12% suffering from minor recurrence only.

Overall, results from definite arterial compression are better than when only an offending vein is found.[10 68 104] In a recent retrospective survey, the authors observed a recurrence rate of 31% in patients with TGN caused by venous compression. In most cases, the recurrence took place within the first 12 months of the operation.[79] Reports of worse outcome after MVD in those patients with a history of previous neuroablative surgery are not substantiated by other studies.[9 10 21 54] Opinions differ as to what is the best policy in cases of recurrence following MVD and both re-exploration and neuroablative procedures have been recommended.[74 80 109] Findings at re-operation are so varied that it is unlikely that any consensus will be arrived at. Perhaps with the advent of imaging, it will be possible to pinpoint the cause of recurrence and decide on the most appropriate course of action.

In experienced hands, MVD is well tolerated. Although in early series a mortality rate of 0.2–1% was described, surgical innovations have since improved the results. In two large recent series consisting of 444[73] and 1995[86] patients, no deaths were reported. Cerebellar injury was reported in 0.45%, eighth nerve injury in 0.8% and CSF leak in 1.85% in a recent retrospective study.[86] However, other centres report higher complication rates.[68 104] It is likely that the results are much better in centres that operate frequently on these patients and have regularly reviewed their technique and improved perioperative monitoring systems.

Although the popularity of MVD has undoubtedly increased in the last two decades, there is ongoing debate regarding its advantages over neurodestructive procedures.[67 126] In the absence of prospective, randomized comparative studies on this issue, the way various surgical treatments are used depends on clinical judgement which inevitable varies across centres.

Radiofrequency gangliolysis

Disillusionment with complications resulting from an uncontrollable spread of alcohol or phenol injected into Meckel's cave for treatment of neuralgia led to the development of thermocoagulation of the Gasserian ganglion in the 1930s. The concept was first explored by Kirchner whose large series was published in 1942.[66] The technique was modified to produce more precise and safer lesions by several authors. In 1974, Sweet presented his method which, by and large, is used today.[124] Essentially, it involves a selective partial lesioning of the affected ganglion or retrogasserian root. Sweet and Wepsic suggested that what resulted from thermocoagulation was selective loss of pain mediating thinly myelinated or non-myelinated fibres.[124] This hypothesis has been challenged by observations that, following this procedure, all sensory functions are found to be affected.[47]

The procedure is carried out in the intermittently anaesthetized patient under fluoroscopic control. The radiofrequency needle is inserted through the foramen ovale into Meckel's cave using bony landmarks. The relationship of the trigeminal rootlets to the foramen ovale is such that by stepwise advancement of the needle the third, second and first divisions will be in succession stimulated, the closer to the clival line the needle tip is (Fig. 4). As soon as the needle has entered Meckel's cave, aspiration will usually yield CSF. Once the needle has travelled the preplanned distance, the patient is allowed to awake, the stylet replaced by the electrode and stimulation of the nerve root carried out. The paraesthesiae elicited must conform to the location of the neuralgia, otherwise the needle must be repositioned. Once appropriate siting has taken place, the patient is anaesthetized again for thermal lesioning. This is performed in cycles of 45 to 90 s at temperatures of 60–90°C. After each lesioning the patient is awakened and manual sensory testing of the face carried out. Additional thermal lesions are performed until clear hypalgesia has ensued.

Use of fluoroscopy, and stepwise increases of needle temperatures make this procedure a relatively safe alternative. Most patients only need an overnight stay. Mortality is virtually nil and severe complications (cerebral haemorrhage, carotid-cavernous fistula, meningitis, and cranial nerve lesions) are very rare.

Unfortunately, this method can cause dysaesthesiae in up to 25%, mostly mild. Dysaesthesiae requiring medical treatment are seen in approximately 8%. Unfortunately, the quality of life in these patients is not improved even if the

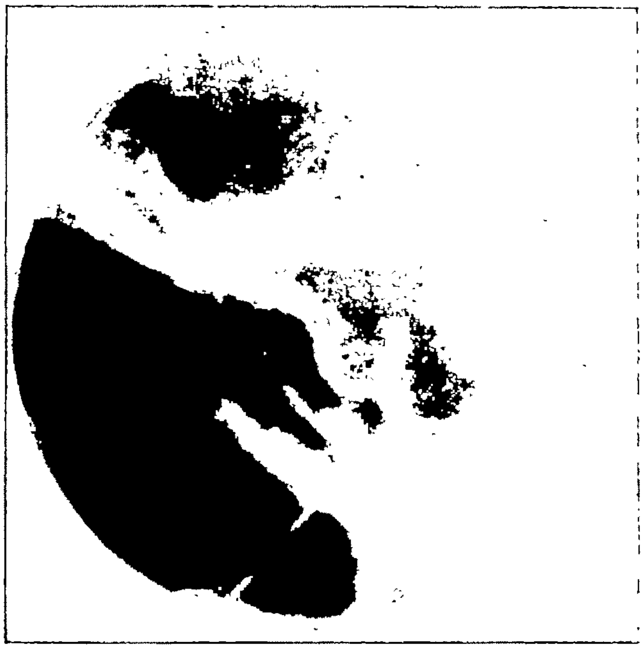

Fig 4 Lateral radiograph of radiofrequency needle inserted into the gasserian ganglion.

original pain has been controlled. There is some indication that this adverse effect is more common in patients with atypical TGN. Frank anaesthesia dolorosa is rare (mostly under 1%). Corneal anaesthesia is a potentially serious complication as it may lead to keratitis in 1–2% of cases. Other rare complications include meningitis, carotid-cavernous fistula, intracranial haemorrhage, and cranial nerve deficits.

The success of pain relief reflects patient selection and the degree of sensory loss the operator is keen to achieve. Zakrzewska identified 38 reports of RFL from the literature, with variable follow-up.[142] The variability in patient selection and follow-up make comparisons very difficult.

We have found three published prospective studies on the long-term efficacy of RFL. Taha and colleagues reported results from a prospective follow-up of 100 patients (from the original group of 154 patients).[126] Those with mild hypalgesia had a recurrence rate of 60% at 3 yr, after which no more recurrencies occurred. Those with deep hypalgesia or actual anaesthesia had a recurrence rate of 20% at 15 yr. No lifetime analysis was provided. Zakrzewska and colleagues reported on 31 patients with pure TGN and 17 with atypical (or 'mixed') TGN in a prospective longitudinal study.[140] In this series, 'pure' TGN patients seem to have the characteristics of the 'typical neuralgia' category whereas 'mixed' neuralgia cases were similar to our 'atypical TGN' category; sensory abnormalities were not mentioned but depression was common in this group.[140] The lifetime analysis indicated a steady increase in the proportion of patients with recurrent pain in both groups. At 3 yr, 40% of both groups complained of recurrent TGN. However, patients belonging to the 'mixed' group reported other facial pain in 75% of cases (while the same was true of 12% of patients with typical TGN).

In a study of 215 patients, the vast majority experienced immediate pain relief (92%).[118] Recurrence of TGN pain occurred in 27% at a mean follow-up of 32 months. The authors did not state the number of patients lost to follow-up. Side effects were similar in intensity and quality to those reported in other series.

Certain conclusions can be drawn from these prospective and retrospective series. Immediate pain relief in typical TGN is high, with diminution of effectiveness over time so that at 3 yr one-third of patients will have recurrent neuralgia. Long-term annoying paraesthesiae following the procedure is experienced by 5–10%, but frank anaesthesia dolorosa is rare. Life-threatening complications occur in less than 1%.

Glycerol gangliolysis

The method was introduced by Håkansson after a fortuitous discovery, during the development of a stereotactic technique for gamma radiation, that glycerol mixed with tantalum powder not only visualized the trigeminal cistern but also abolished pain in patients with trigeminal neuralgia. The first series consisted of 75 patients with a mean follow-up of 18 months.[46] The method was quickly adopted by several centres so that by 1993 over 20 case series had been published describing results in some 2500 patients.[141] The results were rather variable and, in some cases, early enthusiasm was followed by quick disappointment. Several authors have given up the method, either because of poor long-term results or adverse effects[125 135] while advocates of the procedure point out that, with a proper technique, not only is the procedure well tolerated but yields good long-term results .[47]

The procedure can be done under local anaesthesia in fully awake patients, although mild sedation is usually used. The needle is inserted into the trigeminal cistern through the foramen ovale using similar trajectories as in radiofrequency lesioning and balloon compression. Needle positioning must be precise to ensure the tip lies in the ganglion and not the subarachnoid space beneath the temporal lobe.[135] Free CSF flow is the norm, except in previously treated cases. Fluoroscopic control is mandatory but the use of radio opaque contrast (cisternography) to visualize the cistern varies from centre-to-centre. (Håkansson strongly advises its use[47]). Once the needle is optimally placed, the patient is brought into a sitting position and a small test dose of sterile anhydrous glycerol injected. This is followed by small dose increments up to a total of 0.1–0.4 ml, depending on the divisions involved. Some authors argue that the patient's head must be positioned in a specific way to allow the glycerol to reach the intended root. Patients are usually able to perceive the effect of the injection as a tingling or burning sensation in the affected divisions. They remain in the sitting position for 2 h after the injections.

Alhough pain relief is usually immediate, it may take up to 7 days to occur in some patients.[7 135] Most authors report initial pain relief in over 80% of their patients but long term results are highly variable. At 12 months, reported recurrence rates vary from 10 to 53%. At 5 yr, 34–83% of the patients will have experienced recurrence of neuralgia.[36 40 46 117 122 135] The authors differ in their views on the usefulness of repeat lesioning in case of recurrence. Patients with atypical TGN or painful trigeminal neuropathy are likely to have less favourable results.[36 99 119]

This method is generally well tolerated and mortality is negligible. There are anecdotal reports of meningitis, cranial nerve palsies, and local haematomas. Activation of herpes labialis occurs in one third and permanent masseter weakness is seen in a small proportion of patients.[7 99 132]

Although sensory change is usually thought to be limited and not necessary for pain relief,[31 32] Steiger showed that in a series of 122 patients treated with glycerol rhizolysis, post-operative sensory loss was directly correlated with a good long-term outcome.[122] Reports of dysaesthesiae vary from 0 to 44%. This variability may, in part, be a result of many authors including in their series patients previously treated with neuroablative procedures.[99 117 132] Keratitis related to corneal sensory loss is reported in most series although it is very rare.

Glycerol rhizolysis has probably caused more controversy than any other procedure with strong views expressed by both proponents and critics.[36 40 47 125 135] It seems that in centres where this method is commonly used, and the technique meticulously employed, the results are similar to those with other ganglion-level procedures.

Balloon compression

In the 1950s, several groups reported that compression of the ganglion seemed to produce similar, if not better, results compared with the techniques used at the time for root decompression. In 1983, Mullan and Lichtor published their first series of 50 patients who had undergone compression of the trigeminal ganglion using a Fogarty-type balloon.[95] This procedure is performed under general anaesthesia. Using fluoroscopic control, a guide needle is inserted into the foramen ovale, but not beyond it. Through the needle, the Fogarty catheter is advanced until its tip lies in Meckel's cave and the balloon is slowly inflated with 0.5–1.0 ml of contrast dye until it occupies the cave, ensuring adequate compression (Fig. 5). Total compression times vary from 1–6 min.[1 95] This produces only a mild sensory loss with immediate pain relief in practically all patients. Interestingly, masseter weakness is very common although, in most cases, there is complete recovery in a matter of weeks.[95] The patient usually only requires an overnight stay.

This method has been used in both typical and atypical TGN, in patients with MS and in those who have had previous neurodestructive procedures (or MVD) for their TGN.[36 95] Recurrence is reported in 6–14% in the first year. Very few studies employing long-term follow-up are available. In Abdennebi's series, one-third needed re-operation during a mean follow-up of 4.3 yr.[1] Lichtor and Mullan obtained slightly better results in that recurrence was seen in 20% of patients at 5 yr follow-up, and 28% of a small number of patients followed even longer (up to 10 yr).[81]

Troublesome dysaesthesiae following the procedure are reported in all series. Mullan and Lichter comment on 6% of their patients having significant discomfort from these dysaesthesiae and Fraioli and colleagues indicate that 7% required transient medical treatment for the same problem.[36 95] In Abdennebi's series, severe dysaesthesiae were seen in 1.5% and 'moderate' dysaesthesiae in a further 15%.[1] Interestingly, 11% of patients were reported to be discontent or very discontent with the outcome. Many had atypical TGN with dysaesthesia possibly as a result of previous surgery and this dysaesthesia was not relieved by balloon compression.[81]

Stereotactic radiosurgery

Well-localized lesions in the trigeminal nerve can be generated also by stereotactic radiosurgery. Some 50 yr ago, Lars Leksell developed a radiosurgical tool, the so-called 'Gamma Knife', to treat functional brain disorders as an alternative to open intracranial procedures. Among the first patients he treated were two with TGN. However, it took decades before the technique had been refined and imaging developed sufficiently to allow precision targeting for the procedure.[69] Initial attempts at irradiation of the Gasserian ganglion yielded discouraging results. However, in recent years, the target has been the proximal trigeminal root near the pons, with a much improved outcome.[69]

The Gamma Knife is a focused array of 201 intercepting beams of gamma radiation, produced by separate cobalt sources. A stereotactic frame is first secured to the patient's head, followed by MRI to identify the trigeminal nerve. Radiosurgery is carried out with the patient supine with the head under the collimator helmet. Local anaesthesia is used for securing the frame and irradiation is frequently carried out under mild oral or i.v. sedation.[69 70 71]

The dose used is 70–90 Gy. Pain relief is usually not immediate. The mean time to pain relief in two series was approximately one month.[70 134] The histopathological effects of radiosurgery on the trigeminal root were investigated in an experiment performed on two male baboons.[72] Six months after radiosurgery at 80 and 100 Gy, focal axonal degeneration and necrosis were observed. This appears to correlate with contrast enhancement seen on MRI months after radiosurgery. No changes in the ganglion were seen.[72]

In 1996, the first systematic study on the use of stereotactic radiosurgery in TGN was published.[70] Although a multicentre study involving 50 patients, it was designed to evaluate various techniques and radiation doses.

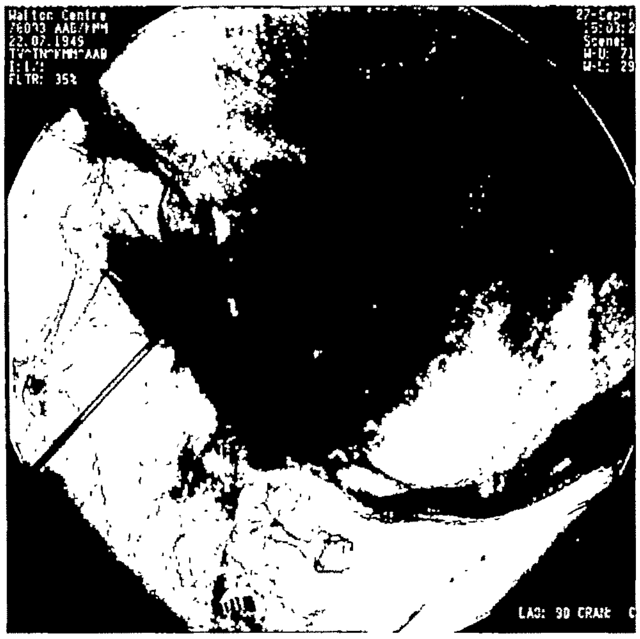

Fig 5 Balloon compression in TGN. Lateral radiograph showing the distended balloon in Meckel's cave. Courtesy of Mr Varma, The Walton Centre for Neurology and Neurosurgery NHS Trust.

Nevertheless, at a median follow-up of 18 months, 58% were pain-free, 36% had significant pain relief, while 6% of procedures were considered to have failed. In two more recent single-centre studies, more favourable results were obtained. Young and colleagues treated 51 patients with TGN with a maximum dose of 70 Gy with excellent immediate effects in 74% and good (pain reduction of more than 50% with or without medication) in 14%.[134] At a mean follow-up of 'more than a year' the incidence of excellent, good and failed relief were 70, 10, and 20%, respectively.[134] In a study involving 106 patients with radiosurgery doses ranging from 70 to 90 Gy, the long-term (median 18 months, range 6–48 months) results were excellent (no pain) 60%, good (50–90% pain reduction) 17%, and poor (less than 50% pain reduction) 24%.[71] In this latter group, only 22 patients had not had previous surgery. The majority had undergone either radiofrequency or glycerol gangliolysis while one-third had undergone MVD. In both studies, side effects were minimal. Facial paraesthesiae were reported in 10%.[71]

This method seems a valuable addition to the existing treatments as it is very patient-friendly and safe. However, as yet, long-term results are lacking and it is not clear which of the other methods can be applied in case of recurrence. Currently, the limiting factor for this treatment is the small number of centres capable of providing this service.

Peripheral neurectomy

Neurectomies of the affected branches were attempted for the first time in the 18th century with variable success. Mainly employed by present day maxillofacial surgeons, the technique is too under-reported to allow evaluation of its usefulness against other treatments. Khanna and Galinde[64] described a successful outcome at 1–5 yr follow-up in 75% of 118 patients who underwent several neurectomies while Mason[84] achieved a success rate of 64% at 12 months and 26% at 4 yr. In a subgroup of 11 patients who had infraorbital neurectomy followed by occlusion of the canal, seven were pain-free at 4 yr. However, he makes a point that, in this retrospective analysis, careful selection of patients was employed conforming to the strictest of TGN criteria. Recently, a small retrospective series was published on 40 patients with typical TGN who underwent this procedure. The majority had previously undergone radiofrequency lesions.[96] At a follow-up of 24 months, six (15%) had experienced a recurrence; these were treated successfully with repeat neurectomies. Surprisingly, none of the above authors discuss adverse effects at all.

By contrast, Danish investigators found that, during a mean follow-up of 7 yr, 78% of patients who had undergone neurectomy experienced a recurrence. One-half of the patients had their first recurrence within a month. In their series, neurectomy (as well as alcohol block) compared unfavourably with radiofrequency lesioning.[102] Complications (mainly eye problems and dysaesthesiae) were reported in just under 10%, similar to those who had undergone radiofrequency lesioning or alcohol blocks.

Neurectomies are performed through an incision made at the eyebrow (supra-orbital nerve) or intraorally (infraorbital, alveolar and lingual nerves). All branches are divided and avulsed under magnification. The relevant foramen is blocked by bone wax, wooden sticks or silicone plugs. The remnant of the nerve may also be cauterized. Despite these efforts, remnants may be found on re exploration and dealing with them in the same way is said to lead to pain relief.[96]

From the existing scarce literature, it cannot be concluded how this procedure sits on the map of TGN management. It does not appear to offer any benefit over other well established surgical procedures, but it may be useful in cases where other treatments have failed and the patient or doctor are reluctant to consider procedures aimed at the ganglion or root.

Cryotherapy

Cryotherapy is a surgical technique in which a peripheral branch of the three major divisions of the trigeminal nerve is exposed and frozen by direct application of a cryoprobe with a tip temperature from –50 to –70°C.[97] The patient requires i.v. sedation or general anaesthesia. Although well tolerated by patients, the results are modest. Of 145 patients who underwent 1–11 sessions of cryotherapy (56% had more than one session), the effect lasted less than 6 months in one half and at 12 months, only 27% were pain-free.[138] Perhaps because of the peripheral approach, the pain broke through in another nerve, requiring a repeat procedure. Almost two-thirds had to remain on their previous medica-

Table 4 Summary of drugs commonly used in TGN. Comments: CBZ, over 90% will respond initially (within 48 h),[141] licensed in UK for TGN; PHT, licensed in UK for TGN, narrow therapeutic range, i.v. treatment possible, therapeutic effect lost quickly, no randomized controlled trials; OXC, licensed for TGN in some countries (not UK), effect similar to CBZ, but better tolerated, cross-allergy with CBZ in 25% cases; LTG, combination therapy with CBZ only shown effective, slow dose escalation with fortnightly dose increments; BAC, best suited for combination therapy, do not withdraw quickly (risk of convulsions)

Drug	Initial dose	Maintenance dose	Adverse effects
Carbamazepine[24 65 98] (CBZ)	200 mg day^{-1}	400–1200 mg day^{-1}	Sedation, dizziness, cognitive impairment, headache, GI symptoms, allergic rash, leucopenia, folate deficiency, hyponatremia, several drug interactions, warfarin!
Oxcarbazepine[137] (OXC)	300 mg day^{-1}	600–1200 mg day^{-1}	Better tolerated than CBZ, sedation, dizziness, cognitive impairment, hyponatremia, rash
Phenytoin[14] (PHT)	300 mg day^{-1}	200–400 mg day^{-1}	Sedation, ataxia, behavioural change, cognitive impairment, lymphadenopathy, osteopenia, acne, gingival hypertrophy, rash, folate deficiency, liver failure, several drug interactions
Lamotrigine[139] (LTG)	25–50 mg day^{-1}	200–400 mg day^{-1}	Allergic rash (necessitates immediate discontinuation), sedation, dizziness, headache, ataxia, significant interactions with other anticonvulsants
Baclofen[37] (BAC)	10 mg day^{-1}	30–80 mg day^{-1}	Sedation, ataxia, fatigue, GI symptoms, muscle weakness

tion. Although improvement in individual nerves was better, from the pain point of view, cryosurgery falls short of results obtained either with procedures aimed at the ganglion or the root.

Some 4% of patients develop post-operative local infection requiring treatment with antibiotics. Frank dyaesthesiae are not common but a sizable proportion of patients, (40%) describe a facial pain which—according to the authors—'does not have the characteristics of TGN or anaesthesia dolorosa'.[138] As in the case of neurectomy, we find little reason to advocate the use of this method except in circumstances where more sophisticated surgical or radiation treatments cannot be carried out.

Alcohol block

Peripheral and ganglionic alcohol blocks have been used since the beginning of the last century but have fallen into disrepute within the neurosurgical and neurological community, mainly because of capricious results and reports of adverse effects.[103 141] Those still employing the technique underline its simplicity and the fact that results are similar to other peripheral ablative procedures. Unfortunately, there is little documentation on the sensory aftermaths of this procedure. In a retrospective analysis of 45 patients treated with one or several alcohol blocks, 84% of patients had a recurrence of pain during the mean follow-up of 8 yr.[102] One-half had a recurrence within a month. As an aftermath, eye problems and dysaesthesiae were reported by 5–8%.[102] In a report of 413 alcohol blocks performed on 82 patients over a period of 22 yr, 'serious' complications were reported in three patients only (cutaneous necrosis, development of bony sequestrium, diplopia).[33] Other complications include facial nerve palsy and loss of vision.[141]

Alcohol injections must be administered directly into the nerve and they are painful and cause local oedema. In our view, the high risk of recurrence of pain combined with a moderate risk of dysaesthetic and other complications exclude this procedure from routine use, except in frail or medically unfit patients, or those who refuse more extensive surgery.

Other peripherally targeted procedures

Other methods of producing controlled peripheral neural trauma include radiofrequency lesions and injections using glycerol, phenol, high concentration tetracaine or a mixture of lignocaine and streptromycin.[44 45 121 131] In all, the average reported pain relief is measured in months and many of these methods are associated with a high number of initial failures. From the existing literature, it is difficult to draw conclusions as to their true efficacy, but it is doubtful whether they ever provide long-lasting benefit. Authors advocating the use of these measures frequently quote failure rates or complications from other, more invasive treatments that do not accurately reflect the current literature.

Pharmacotherapy

In general agreement, pharmacotherapy remains the mainstay of treatment of TGN despite the fact that only few randomized controlled trials have been conducted.[35 142] Carbamazepine has been compared with placebo in three separate studies, involving a total of 151 patients[24 65 98] with a good initial effect in approximately 70%. The NNT (number-needed-to-treat) for effective pain control (>50% pain relief compared with placebo) from these three studies is 2.6, while NNH (number-needed-to-harm; i.e., adverse effects in excess to those seen with placebo) is about 3.4.[87] These studies, and its subsequent wide-spread use in TGN, made carbamazepine something of a gold standard against which other drugs have been compared in subsequent controlled trials. These drugs include tizanidine, baclofen,

Table 5 Choice of treatment of TGN—based on anticipated efficacy (Nurmikko and Eldridge, unpublished). GENERAL. (1) No preference between pharmacotherapy and surgery—the patient is entitled to a balanced and dispassionate explanation of the treatments available. (2) Patient to be informed that large case series published only on MVD and gangliolysis. (3) Pain relief, risks, recurrence rate, adverse effects must be discussed. (4) Peripheral procedures recommended mainly for those in whom other procedures contraindicated, or patient refuses more extensive surgery. (5) If posterior fossa exploration negative, partial rhizotomy at the operator's discretion. (6) In patients with MS, the same rules apply as in TGN in general. (7) In patients with co-existing tumour, surgical removal, or radiotherapy remain the first-line treatment. (8) Note that type of pain is decisive in choosing between treatments. (+++ good long-term outcome likely, ++ moderate-to-good initial result, moderate-to-high recurrence rate, + partial or transient pain relief possible, – not recommended, risk-benefit ratio poor, † risk of dysaesthesiae) *MVD (including partial root section); **radiofrequency lesion, glycerolysis, balloon compression

	MVD(PRS)*	**gangliolysis****	**radiosurgery**	**peripheral**	**medication**
(a) *New cases*					
TGN typical/MRTA +ve	+++	++†	++	+†	++(+)
/MRTA –ve	++	++†	++	+†	++
TGN atypical/MRTA+ve	+	+†	++	–	++
/MRTA –ve	–	+†	?	–	+
Trigeminal neuropathy/MRTA+ve	(+)	–	–	–	+
MRTA –ve	–	–	–	–	+
(b) *Recurrence of pain*					
TGN typical/MRTA+ve	+++	++†	++	+†	++
/MRTA –ve	+	++†	++	+†	++
TGN atypical/MRTA +ve	+	+†	?	–	++
/MRTA –ve	–	+†	?	–	+
TGN atypical/major sensory loss	–	–	–	–	+
Trigeminal neuropathy/MRTA +ve	(+)	–	–	–	+
/MRTA –ve	–	–	–	–	+

pimozide, tocainade, and oxcarbazepine.[37 77 82 130 137] While none have been shown to be superior to carbamazepine, the small number of patients evaluated in individual trials (usually less than 20) precludes firm judgement in this regard. Table 4 lists the drugs most commonly used in this condition.

Considering the complexities of the pathophysiology of TGN (atypical TGN included) and the narrow mechanism of action of the drugs available, combination treatments seem a natural choice. However, there are no published studies comparing directly polytherapy with monotherapy.

The long-term effects of carbamazepine have been evaluated in one study only, showing either loss of effect or problems with tolerability in one half of patients over 10 yr.[128] Loss of effect can be compensated to a degree by adding lamotrigine.[139] However, lamotrigine poses the problem of slow dose escalation, which may be inconvenient to a patient with sudden increase in TGN pain.

Baclofen alone seems to have a moderate effect on TGN only, and its long-term efficacy remains in doubt.[37] One weak study suggests that clonazepam is of value but, in our hands, it has been disappointing as most patients with good initial response quickly recognize that the effect is lost.[23] Anecdotally, several patients have been treated by ourselves with the combination of carbamazepine or lamotrigine and gabapentin. Doses needed are usually in the low-to-moderate range (carbamazepine 400–800 mg day^{-1}; lamotrigine 200–400 mg day^{-1}; gabapentin 900–1200 mg day^{-1}), which are usually well tolerated by patients, and preferred to monotherapy with high doses of carbamazepine alone.

Using these drugs requires a good understanding of their pharmacokinetics, metabolism, and interactions. There are several good reviews available.[34 141]

Which treatment to choose first?

With considerable amount of information about TGN readily available, many patients and their relatives are keen to consider surgery as first-line treatment, in anticipation of a permanent cure. It is, therefore, imperative for the doctor to have an understanding of the relative efficacy of various treatments, including complications and recurrence rates. Our policy is to view requests of early surgical treatment with sympathy, even if the patient responds well to pharmacotherapy, but to ensure that he has a realistic view of what it entails.

Table 5 summarizes our current thinking with respect to preferred treatments in individual cases. We emphasize that it reflects only our experience and conclusions we have drawn from the often conflicting literature. As long as there is no evidence-based medicine to guide treatment choice, the doctor will have to combine theory with clinical experience in as balanced a way as possible.

References

1 Abdennebi B, Mahfouf L, Nedjahi T. Long-term results of percutaneous compression of the Gasserian ganglion in trigeminal neuralgia. *Stereotact Funct Neurosurg* 1997; **68**: 190–5

2 Adams CBT. Microvascular compression: an alternative view and hypothesis. *J Neurosurg* 1989; **57**: 1–12

3 Adams CBT. Trigeminal neuralgia: pathogenesis and treatment. *Br J Neurosurg* 1997; **11**: 493–5

4 Ameli NO. Avicenna and trigeminal neuralgia. *J Neurol Sci* 1965; **2**: 105–7

5 Amir R, Devor M. Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. *Neuroscience* 2000; **95**: 189–95

6 Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999; **19**: 8589–96

7 Arias MJ. Percutaneous retrogasserian glycerol rhizotomy for trigeminal neuralgia. A prospective study of 100 cases. *J Neurosurg* 1986; **65**: 32–6

8 Baldwin NG, Sahni KS, Jensen ME, Pieper DR, Anderson RL, Young HF. Association of vascular compression in trigeminal neuralgia versus other 'facial pain syndromes' by magnetic resonance imaging. *Surg Neurol* 1991; **36**: 447–52

9 Barba D, Alksne JF. Success of microvascular decompression with and without prior surgical therapy for trigeminal neuralgia. *J Neurosurg* 1984; **60**: 104–7

10 Barker FG, Jannette PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med* 1996; **334**: 1077–83

11 Beaver DL. Electron microscopy of the Gasserian ganglion in trigeminal neuralgia. *J Neurosurg* 1967; **26**: 138–50

12 Bergouignan M. Cures heureuses de névralgies faciales essentielles par le diphennyl-hydantoinate de soude. *Rev Laryngol Otol Rhinol (Bord)* 1942; **63**: 34–41

13 Boecher-Schwarz HG, Bruehl K, Kessel, Guenthner M, Perneczky A, Stoeter P. Sensitivity and specificity of MRA in the diagnosis of neurovascular compression in patients with trigeminal neuralgia. A correlation of MRA and surgical findings. *Neuroradiology* 1998; **40**: 88–95

14 Braham J, Saia A. Phenytoin in the treatment of trigeminal and other neuralgias. *Lancet* 1960; **ii**: 892–3

15 Brisman R. Trigeminal neuralgia and multiple sclerosis. *Arch Neurol* 1987; **44**: 379–81

16 Broggi G, Ferroli P, Franzini A, Servello D, Dones I. Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; **68**: 59–64

17 Broggi G, Ferroli P, Franzini A, Pluderi M, La Mantia L, Milanese C. Role of microvascular decompression in trigeminal neuralgia and multiple sclerosis. *Lancet* 1999; **354**: 1878–9

18 Bowsher D, Miles JB, Haggett CE, Eldridge PR. Trigeminal neuralgia: a quantitative sensory perception threshold study in patients who had not undergone previous invasive procedures. *J Neurosurg* 1997; **86**: 190–2

19 Bullit E, Tew JM, Boyd J. Intracranial tumors in patients with facial pain. *J Neurosurg* 1986; **64**: 865–71

20 Burchiel KJ, Slavin KV. On the natural history of trigeminal neuralgia. *Neurosurgery* 2000; **46**: 152–5

21 Burchiel KJ, Clarke H, Haglund M, Loeser JD. Long-term efficacy of microvascular decompression in trigeminal neuralgia. *J Neurosurg* 1988; **69**: 35–8

22 Burton M, Onofrio MD. Radiofrequancy percutaneous Gasserian ganglion lesions. Results in 140 patients with trigeminal pain. *J Neurosurg* 1975; **42**: 132–9

23 Caccia MR. Clonazepam in facial neuralgia and cluster headache. *Eur Neurol* 1975; **13**: 560–3

24 Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbamazepine (Tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1966; **29**: 265–7

25 Canavero S, Bonicalzi V, Pagni CA. The riddle of trigeminal neuralgia. Letter. *Pain* 1995; **60**: 229–30

26 Cheng TMW, Cascino TL, Onofrio BM. Comprehensive study of diagnosis and treatment of trigeminal neuralgia secondary to tumours. *Neurology* 1993; **43**: 2298–302

27 Clifford DR, Trotter IL. Pain in multiple sclerosis. *Arch Neurol* 1984; **41**: 1270–2

28 Cruccu G, Leandri M, Feliciani M, Manfredi M. Idiopathic and symptomatic trigeminal pain. *J Neurol Neurosurg Psychiatry* 1990; **53**: 1034–42

29 Dandy WE. Section of sensory root of the trigeminal nerve at the pons. *Bull Johns Hopkins Hosp* 1925; **36**: 105

30 Eide PK, Rabben T. Trigeminal neuropathic pain: pathophysiological mechanisms examined by quantitative assessment of abnormal pain and sensory perception. *Neurosurgery* 1998; **43**: 1103–10

31 Eide PK, Rabben T, Skjelbred P, Stubhaug A. The effect of peripheral glycerol on trigeminal neuropathic pain examined by quantitative assessment of abnormal pain and sensory perception. *Acta Neurochir* 1998; **140**: 1271–7

32 Eide PK, Stubhaug A. Sensory perception in patients with trigeminal neuralgia: effects of percutaneous retrogasserian glycerol rhizotomy. *Stereotact Funct Neurosurg* 1997; **68**: 207–11

33 Fardy MJ, Patton DW. Complications associated with peripheral alcohol injections in the management of trigeminal neuralgia. *Br J Oral Maxillofac Surg* 1994; **32**: 387–91

34 Feely M. Drug treatment of epilepsy. *BMJ* 1999; **318**: 106–9

35 Fields HL. Treatment of trigeminal neuralgia. *N Engl J Med* 1996; **334**: 1125–6

36 Fraioli F, Esposito V, Guidetti B, Cruccu G, Mangfredi M. Treatment of trigeminal neuralgia by thermocoagulation, glycerolization, and percutaneous compression of the gasserian ganglion and/or retrogasserian rootlets: long-term results and therapeutic protocol. *Neurosurgery* 1989; **24**: 239–45

37 Fromm GH, Terrence CF, Chatta AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow up. *Ann Neurol* 1984; **15**: 240–4

38 Fromm GH, Graff-Radford SB, Terrence CF, Sweet WH. Pre-trigeminal neuralgia. *Neurology* 1990; **40**: 1493–5

39 Fromm GH, Sessle BJ. Introduction and historical review. In: Fromm GH, Sessle B, eds. *Trigeminal Neuralgia. Current Concepts Regarding Pathogenesis and Treatment.* Boston: Butterworth-Heinemann, 1991; 1–26

40 Fujimaki T, Fukushima T, Miyazaki S. Percutaneous retrogasserian glycerol injection in the management of trigeminal neuralgia: long-term results. *J Neurosurg* 1990; **73**: 212–6

41 Gardner WJ, Miklos MV. Response of trigeminal neuralgia to 'decompression' of sensory root: discussion of cause of trigeminal neuralgia. *JAMA* 1959; **170**: 1773–6

42 Gass A, Kitchen N, MacManus DG, Moseley IF, Hennerici MG, Miller DH. Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with magnetic resonance imaging. *Neurology* 1997; **49**: 1142–4

43 Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain* 1997; **120**: 193–203

44 Goto F, Ishizaki K, Yoshikawa D, Obata H, Arii H, Terada M. The long lasting effects of peripheral nerve blocks for trigeminal neuralgia using a high concentration of tetracaine dissolved in bupivacaine. *Pain* 1999; **79**: 101–3

45 Gregg JM, Small EW. Surgical management of trigeminal pain with radiofrequency lesions of peripheral nerve. *J Oral Maxillofac Surg* 1986; **44**: 122–5

46 Håkansson S. Trigeminal neuralgia treated by the injection into the trigeminal cistern. *Neurosurgery* 1981; **9**: 638–46

47 Håkansson S. Comparison of surgical treatments for trigeminal neuralgia: re-evaluation of radiofrequency rhizotomy (letter). *Neurosurgery* 1997;

48 Hamlyn PJ, King TJ. Neurovascular compression in trigeminal neuralgia: a clinical and anatomical study. *J Neurosurg* 1992; **76**: 948–52

49 Hampf G, Bowsher D, Wells C, Miles J. Sensory and autonomic measurements in idiopathic trigeminal neuralgia: differentiation from some other causes of facial pain. *Pain* 1990; **40**: 241–8

50 Hardy DG, Rhoton AL Jr. Microsurgical relationships of the superior cerebellar artery and trigeminal nerve. *J Neurosurg* 1978; **49**: 669–78

51 Harris W. Rare forms of paroxysmal trigeminal neuralgia and their relation to disseminated sclerosis. *BMJ* 1950; **2**: 1015–9

52 Huang C-F, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for trigeminal schwannomas. *Neurosurgery* 1999; **45**: 11–16

53 Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology* 1995; **45**: 1294–6

54 Hunn MK, Eldridge PR, Miles JB, West B. Persistent facial pain following microvascular decompression of the trigeminal nerve. *Br J Neurosurg* 1998; **12**: 23–8

55 Ischia S, Luzzani A, Polate E. Retrogasserian glycerol injection: a retrospective study of 112 patients. *Clin J Pain* 1990; 6291–6

56 Jääskeläinen SK, Forssell H, Tenovuo O. Electrophysiological testing of the trigeminofacial system: aid in the diagnosis of atypical facial pain. *Pain* 1999; **80**: 191–200

57 Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW, the CHAMPS Study group. *N Engl J Med* 2000; **343**: 898–904

58 Jannetta PJ. Treatment of trigeminal neuralgia by suboccipital and transtentorial cranial operation. *Clin Neurosurg* 1977; **24**: 538–49

59 Javadpour M, Nurmikko T, Eldridge P, Miles J. Submitted 2001.

60 Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological studies. *Acta Neurol Scand* 1982; **65**: 182–189.

61 Katusic S, Beard CM, Bergstrahl E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesoata 1945–1984. *Ann Neurol* 1990; **27**: 89–95

62 Kerr FWL, Miller RH. The pathology of trigeminal neuralgia. Electron microscopic studies. *Arch Neurol* (*Chicago*) 1966; **15**: 308–15

63 Kerr FWL. Pathology of trigeminal neuralgia: light and electron microscopic observations. *J Neurosurg* 1967; **26**: 151–6

64 Khanna JN, Galinde JS. Trigeminal neuralgia. Report of 140 cases. *Int J Oral Surg* 1985; **14**: 325–2

65 Killian JM, Fromm GH. Carbamazepine in the treatment of neuralgia. *Arch Neurol* 1968; **19**: 129–36

66 Kirschner M. Die Behandlung der Trigeminusneuralgie (nach Erfahrungen an 1113 Kranken). *Münch Med Wschr* 1942; **89**: 235–9

67 Kitt CA, Gruber K, Davis M, Woolf CJ, Levine JD. Trigeminal neuralgia: opportunities for research and treatment. *Pain* 2000; **85**: 3–7

68 Kolluri S, Heros RC. Microvascular decompression for trigeminal neuralgia. A five year follow-up study. *Surg Neurol* 1984; **22**: 235–240

69 Kondziolka D. Functional neurosurgery. *Neurosurgery* 1999; **44**: 12–20

70 Kondziolka D, Lunsford LD, Flickinger JC, Young R, Vermeulen S, Duma C, Jacques D, Rand RW, Regis J, Peragut JC, Manera L, Epstein M, Lindquist C. Steretotactic radiosurgery for trigeminal neuralgia: a multi-institution study using the gamma unit. *J Neurosurg* 1996; **84**: 940–5

71 Kondziolka D, Perez P, Flickinger JC, Habeck M, Lunsford LD. Gamma knife radiosurgery for trigeminal neuralgia. *Arch Neurol* 1998; **55**: 1524–9

72 Kondziolka D, Lacomis D, Niranjan A, Mori Y, Maesawa S, Felows W, Lunsford LD. Histological effects of trigeminal nerve radiosurgery in a primate model: implications for trigeminal neuralgia radiosurgery. *Neurosurgery* 2000; **64**: 971–7

73 Kondo A. Follow-up results of microvascular decompression in trigeminal neuralgia and hemifacial spasm. *Neurosurgery* 1997; **40**: 46–52

74 Kureshi SA, Wilkins RH. Posterior fossa exploration for persistent or recurrent trigeminal neuralgia or hemifacial spasm: surgical findings and therapeutic implications. *Neurosurgery* 1998; **43**: 1111–7

75 Leandri M, Parodi CI, Favale E. Early trigeminal evoked potentials in tumours of the base of the skull and trigeminal neuralgia. *Electroenceph Clin Neurophysiol* 1988; **71**: 114–24

76 Leandri M, Eldridge P, Miles J. Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia. *Neurology* 1998; **51**: 1641–6

77 Lechin F, van der Dijs B, Lechin ME. Pimozide therapy for trigeminal neuralgia. *Arch Neurol* 1989; **49**: 960–3

78 Lee KH, Chang JW, Park YG, Chung SS. Microvascular decompression and percutaneous rhizotomy in trigeminal neuralgia. *Stereotact Funct Neurosurg* 1997; **68**: 196–9

79 Lee SH, Levy EI, Scarrow AM, Kassam A, Jannetta PJ. Recurrent trigeminal neuralgia attributable to veins after microvascular decompression. *Neurosurgery* 2000; **46**: 356–2

80 Liao J-J, Cheng W-C, Chang C-N, Wei K-C, Hsu Y-H, Lin T-K. Reoperation for recurrent trigeminal neuralgia after microvascular decompression. *Surg Neurol* 1997; **47**: 562–70

81 Lichtor T, Mullan JF. A 10-year follow-up review of percutaneous microcompression of the trigeminal ganglion. *J Neurosurg* 1990; **72**: 49–54

82 Lindström P, Lindblom U. The analgesic effect of tocainide in trigeminal neuralgia. *Pain* 1987; **28**: 45–50

83 Liu C-H, Wall PD, Ben-Dor E, Michaelis M, Devor M. Tactile allodynia in the absence of C-fibre activation: altered firing properties of DRG neurons following spinal nerve injury. *Pain* 2000; **85**: 503–21

84 Mason DA. Peripheral neurectomy in the treatment of trigeminal neuralgia of second and third divisions. *J Oral Surg* 1972; **30**: 113–20

85 Masur H, Papke K, Bongartz G, Vollbrecht K. The significance of three-dimensional MR-defined neurovascular compression for the pathogenesis of trigeminal neuralgia. *J Neurol* 1995; **242**: 93–8

86 McLaughlin MR, Jannetta PJ, Clyde BL, Subach BR, Comey CH, Resnick DK. Microvascular decompression of cranial nerves: lessons learned after 4400 operations. *J Neurosurg* 1999; **90**: 1–8

87 McQuay H, Carrol D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ* 1995; **311**: 1047–52

88 Meaney JF, Eldridge PR, Dunn LT, Nixon TE, Whitehouse G, Miles JB. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. Comparison of surgical findings in 52 consecutive operative cases. *J Neurosurg* 1995; **83**: 799–805

89 Meaney JF, Watt JW, Eldridge PR, Whitehouse GH, Wells JC, Miles JB. Association between trigeminal neuralgia and multiple sclerosis: role of magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 1995; **59**: 253–9

90 Melzack R, Terrence C, Fromm G, Amsel R. Trigeminal neuralgia and atypical facial pain: use of McGill Pain Questionnaire for discrimination and diagnosis. *Pain* 1986; **27**: 297–302

91 Merskey H, Bogduk N. Classification of chronic pain. *Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle: IASP Press, 1994; 59–71

92 Miles JB, Eldridge PR, Haggett CE, Bowsher D. Sensory effects of microvascular decompresion in trigeminal neuralgia. *J Neurosurg* 1997; **86**: 193–6

93 Mittal B, Thomas DGT. Controlled thermocoagulation in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1986; **49**: 932–6

94 Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology* 1988; **38**: 1830–4

95 Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. *J Neurosurg* 1983; **59**: 1007–12

96 Murali R, Rovit RL. Are peripheral neurectomies of value in the treatment of trigeminal neuralgia? An analysis of new cases and cases involving previous radiofrequency gasserian thermocoagulation. *J Neurosurg* 1996; **85**: 435–7

97 Nally FF. A 22-year study of paroxysmal trigeminal neuralgia in 211 patients with a 3-year appraisal of the role of cryotherapy. *Oral Surg* 1984; **58**: 17–23

98 Nicol CF. A four week double blind study of tegretol in facial pain. *Headache* 1969; **9**: 54–7

99 North RB, Kidd DH, Piantadosi S, Carson BS. Percutaneous retrogasserian glycerol rhizotomy. Predictors of success and failure in treatment of trigeminal neuralgia. *J Neurosurg* 1990; **72**: 851–6

100 Nurmikko TJ. Altered cutaneous sensation in trigeminal neuralgia. *Arch Neurol* 1991; **48**: 523–7

101 Nurmikko T, Haggett C, Miles J. Neurogenic vasodilatation in trigeminal neuralgia. In: Devor M, Rowbotham MC, Wiesenfeld-Hallin, eds. *Proceedings of the 9th World Congress on Pain. Progress in Pain Research and Management.* Vol. 16. Seattle: IASP Press, 2000; 747–55

102 Oturai AB, Jensen K, Erikson J, Marsden F. *Neurosurgery* for trigeminal neuralgia: Comparison of alcohol block, neurectomy and radiofrequency coagulation. *Clin J Pain* 1996; **12**: 311–15

103 Peet MM, Schneider RC. Trigeminal neuralgia. A review of six hundred and eighty nine cases with a follow up study on sixty five per cent of the group. *J Neurosurg* 1952; **9**: 367–7

104 Platt JH, Wilkins RH. Treatment of tic douloureux and hemifacial spasm by posterior fossa exploration: therapeutic implications of various neurovascular relationships. *Neurosurgery* 1984; **14**: 462–71

105 Rappaport ZH, Devor M. Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. *Pain* 1994; **56**: 127–38

106 Rappaport ZH, Govrin-Lippmann R, Devor M. An electron-microscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. *Stereotact Funct Neurosurg* 1997; **68**: 182–6

107 Rasmussen P, Riiishede J. Facial pain treated with carbamazepine (Tegretol). *Acta Neurol Scand* 1970; **46**: 385–408

108 Rasmussen P. Facial pain. A prospective survey of 1052 patients with a view of: definition, classification, delimitation, general data, genetic factors and previous diseases. *Acta Neurochir* 1990; **107**: 112–20

109 Rath SA, Klein HJ, Richter H-P. Findings and long-term results of subsequent operations after failed microvascular decompression for trigeminal neuralgia. *Neurosurgery* 1996; **39**: 933–40

110 Resnick DK, Levu EI, Jannetta PJ. Microvascular decompression for pediatric onset trigeminal neuralgia. *Neurosurgery* 1998; **43**: 804–8

111 Rhoton AL. The cerebellopontine angle and posterior fossa cranial nerves by the retrosigmoid approach. *Neurosurgery* 2000; **47** (Suppl): S93–129

112 Rockliff BW, Davis EH. Controlled sequential trials of carbamazepine in trigeminal neuralgia. *Arch Neurol* 1966; **15**: 129–136

113 Rose FC. Trigeminal neuralgia. *Arch Neurol* 1999; **56**: 1163–4

114 Roski RA, Horwitz SJ, Spetzler RF. Atypical trigeminal neuralgia in a 6 year old boy. *J Neurosurg* 1982; **5**: 424–5

115 Rushton JG, Olafson A. Trigeminal neuralgia associated with multiple sclerosis. *Arch Neurol* 1965; **13**: 383–5

116 Sahni KS, Pieper DR, Anderson R, Baldwin NG. Relation of hypesthesia to the outcome of glycerol rhizolysis for trigeminal neuralgia. *J Neurosurg* 1990; **72**: 55–8

117 Saini SS. Retrogasserian glycerol injection therapy in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1987; **50**: 1536–8

118 Scrivani SJ, Keith DA, Mathews ES, Kaban LB. Percutaneous stereotactic differential radiofrequency thermal rhizotomy for the treatment of trigeminal neuralgia. *J Oral Maxillofac Surg* 1999; **57**: 104–11

119 Slettebø H, Hirschberg H, Lindegaard KF. Long-term results after percutaneous retrogasserian glycerol rhizotomy in patients with trigeminal neuralgia. *Acta Neurochir* 1993: **122**: 231–5

120 Slettebø HJ, Eide PK. A prospective study of microvascular decompression for trigeminal neuralgia. *Acta Neurochir* 1997; **139**: 421–5

121 Stajic Z, Juniper RP, Todorovic L. Peripheral streptomycin/lidocaine injections versus lidocaine alone in the treatment of idiopathic trigeminal neuralgia. A double blind controlled trial. *J Craniomaxillofac Surg* 1990; **18**: 243–6

122 Steiger HJ. Prognostic factors in the treatment of trigeminal neuralgia. Analysis of a differential therapeutic approach. *Acta Neurochir* 1991; **113**: 11–17

123 Stenager E, Knudsen L, Jensen K. Acute and chronic pain in multiple sclerosis. *Acta Neurol Scand* 1991; **84**: 197–200

124 Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibres. Part 1: trigeminal neuralgia. *J Neurosurg* 1974; **39**: 143–56

125 Sweet WH, Poletti CE. Problems with retrogasserian glycerol in the treatment of trigeminal neuralgia. *Appl Neurophys* 1985; **48**: 252–7

126 Taha JM, Tew JM, Buncher CR. A prospective 15-year follow up of 154 consecutive patients with trigeminal neuralgia treated by percutaneous stereotactic radiofrequency thermal rhizotomy. *J Neurosurg* 1995; **83**: 989–93

127 Tash RR, Sze G, Leslie DR. Trigeminal neuralgia: MR imaging features. *Radiology* 1989; **172**: 767–70

128 Taylor JC, Brauer S, Espir MLE. Long-term treatment of trigeminal neuralgia with carbamazepine. *Postgrad Med J* 1981; **57**: 6–18

129 Tenser RB. Trigeminal neuralgia. Mechanisms and treatment. *Neurology* 1998; **51**: 17–19

130 Vilming ST, Lyberg T, Lataste X. Tizanide in the management of trigeminal neuralgia. *Cephalagia* 1986; **6**: 181–2

131 Wilkinson HA. Trigeminal nerve peripheral branch phenol/glycerol injections for tic douloureux. *J Neurosurg* 1999; **90**: 828–32

132 Waltz TA, Dalessio DJ, Copeland B, Abbott G. Percutaneous injection of glycerol for the treatment of trigeminal neuralgia. *Clin J Pain* 1989; **5**: 195–8

133 Yoon KB, Wiles JR, Miles JB, Nurmikko TJ. Long-term outcome of percutaneous thermocoagulation in trigeminal neuralgia. *Anaesthesia* 1999; **54**: 803–8

134 Young RF, Vermeules SS, Grimm P, Blasko J, Posewitz A. Gamma knife radiosurgery for treatment of trigeminal neuralgia. Idiopathic and tumor related. *Neurology* 1997: 48: 608–14

135 Young RF. Glycerol rhizolysis in the treatment of trigeminal neuralgia. *J Neurosurg* 1988; **69**: 39–45

136 Pieper DR, Dickerson J, Hassenbush SJ. Percutaneous retrogasserian glycerol rhizolysis for treatment of chronic intractable cluster headaches: long-term results. *Neurosurgery* 2000; **46**: 369 (Comment by Young RF)

137 Zakrzewska JM, Patsalos PN. Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1989; **52**: 472–476

138 Zakrzewska JM, Nally FF. The role of cryotherapy (cryoanalgesia) in the management of paroxysmal trigeminal neuralgia: a six year experience. *Br J Oral Maxillofac Surg* 1988; **26**: 18–25

139 Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997; **73**: 223–30

140 Zakrzewska JM, Jassim S, Bulman JS. A prospective, longitudinal study on patients with trigeminal neuralgia who underwent radiofrequency thermocoagulation of the Gasserian ganglion. *Pain* 1999; **79**: 51–8

141 Zakrewska JM. *Trigeminal Neuralgia*. London: WB Saunders, 1995.

142 Zakrewska JM. Trigeminal, eye and ear pain. In: Wall PD, Melzack R, eds. *Texbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999; 739–752

143 http://www.i-h-s.org/ihsnew/frameset.htm

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Chronic opioid therapy for non-cancer pain

B.-J. Collett

Pain Management Service, University Hospitals of Leicester, Leicester Royal Infirmary, Leicester LE1 5WW, UK

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Opioids are the most potent and effective analgesics available and have become accepted as appropriate treatment for acute and cancer pain. However, there is concern regarding their usage in chronic non-cancer pain because of fears that they are ineffective in the long-term, that their use will lead to a deterioration in the patient's condition and that the medical prescription of opioids will lead to an increase in their non-medical use within society. In certain countries, physicians may also fear triggering scrutiny and sanctions by regulatory agencies when prescribing long-term opioids for chronic pain of non-malignant origin.[18 48 92] However, relief of pain is a humanitarian issue and it has been said that 'to leave a person in avoidable pain and suffering should be regarded as a serious breach of fundamental human rights'.[87]

Epidemiology of chronic pain

Chronic pain is a common complaint within the community and a common cause of distress and disability. A telephone survey of 1037 randomly selected households in the UK concluded that, out of a total household population of 2942 individuals, 208 adults (7%) experienced intermittent or persistent pain from non-fatal causes that lasted for at least 3 months.[8] Fifty-five per cent stated they were unable to lead a normal life because of the pain. A recent Scottish study indicated a higher incidence of chronic pain or discomfort (46.5%) in the community.[27] Half of those in pain had severe or disabling pain. Back pain and arthritis were the most common causes of pain, accounting for one-third of all complaints. Chronic pain was associated with older age, retirement, or inability to work. Other studies amply demonstrate that recurrent and chronic pain is a major public health problem.[24] Poor management of such pain has important consequences for individual patients, their families, and society.

Epidemiology of opioid use for chronic non-cancer pain

Sorenson and colleagues investigated the use of opioids outside hospitals in Denmark.[88] Their sample of 480 000 represented almost 10% of the Danish population. During the 1-month study period, strong opioids were prescribed to 633 patients (0.2% population). In 110 patients (17%), the indication was pain as a result of malignancy. In 387 patients (58%), the indication was for chronic non-malignant painful conditions, which included back pain (25%), headache (10%), arthritis (9%), pancreatitis (6%), angina pectoris (5%), and phantom pain (5%). In 69 patients, strong opioid was prescribed for recurrent acute pain—the most common indication being migraine. They concluded that only a small number of patients with chronic pain within the community (estimated prevalence 30%) were being treated with strong opioids.

In Australia, over a 10-yr period from 1986 to 1996, the amount of oral morphine consumed for pain control increased fivefold from 117 to 578 kg. Use in non-malignant pain accounted for much of this increase. In a sample of patients being treated with opioids for non-cancer pain, one-third continued using opioids for 5 yr or more and this usage was associated with dose escalation. Many patients had poorly defined medical problems and social and emotional problems were common.[6]

There have been several surveys of opioid prescribing habits for non-malignant pain amongst pain management specialists. In the UK, Coniam surveyed physician members of the Intractable Pain Society regarding opioid prescription for non-malignant pain. Sixty-two per cent of respondents indicated that they did prescribe opioids for non-malignant pain, the predominant reason being failure of other treatments. However, 81% reported some problems with patients on long-term opioid therapy, the most frequent being intolerance to side effects, which was reported by 63.8% of respondents.[23] The Clinical Standards Advisory Group (CSAG) study 'Services for patients with pain' reported

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Table 1 Overall outcome of RCTs on opioid therapy for different chronic non-cancer pain syndromes.[37] +=positive effect; –=no effect; #=significant adverse effects (adapted from Graven *et al.*[37])

Pain type	Reference	Control	Results
Nociceptive	Arner and Meyerson[3]	placebo	+
	Kjaersgaard-Andersen and colleagues[49]	paracetamol	+#
Neuropathic	Arner and Meyerson[3]	placebo	–
	Dellemijin and Vanneste[26]	placebo/diazepam	+
	Kupers and colleagues[52]	placebo	+
	Rowbotham and colleagues[76]	placebo/lignocaine	+
Idiopathic	Arner and Myerson[3]	placebo	–
	Kupers and colleagues[52]	placebo	–
	Moulin and colleagues[60]	benztropine	+#
Unspecified	Arkinstall and colleagues[2]	placebo	+#
	Mays and colleagues[55]	bupivacaine/placebo	+

that 75% of pain management clinics in the UK currently provide supervised opioid therapy for non-cancer pain.[19]

Turk and Brody surveyed members of the American Pain Society and reported that 83% maintained some patients on opioid therapy. Generally, the respondents believed that opioids were under-utilized and that addiction was over-emphasized.[92]

However, pain specialists do not treat most patients with pain. A random sample of 6962 American doctors from seven specialities (excluding pain management) suggested that the respondents (1912 doctors) relatively infrequently prescribed opioids for patients with chronic non-cancer pain.[91] Rheumatologists treated more chronic pain patients and prescribed long-term opioids more frequently than any other speciality in the survey.

The triggers for a doctor to prescribe opioids for a particular patient requires further investigation. Data from patients attending a pain treatment centre suggest that prescribing practice did not appear to be influenced either by the extent of pathology or by pain severity. Patients who displayed high levels of observable pain behaviours and reported high levels of functional impairment were significantly more likely to be prescribed opioids.[93]

There is a clinical impression in the UK that opioids are only given as a last resort. Yet in 1995, 4.13 million prescriptions for opioids were written in England alone.

Are opioids effective for chronic non-cancer pain?

Published patient surveys and case-reports support the efficacy and safety of long-term opioid analgesics in carefully selected patients with chronic non-malignant nociceptive and neuropathic pain.[7,35,68,84,89,90,96,102] Patients themselves report positive preference for opioid medication.[2,45,98]

A criteria-based methodological assessment of eight randomized controlled trials (RCT) of efficacy of opioids in non-malignant pain has recently been reported.[37] Methodological quality of the trials was assessed and agreed by three independent reviewers against 14 criteria and the types of pain (nociceptive, neuropathic, or idiopathic) studied in each trial were identified (Table 1). Some of these trials are infusion or injection studies and some are longer-term studies of oral or sublingual opioids.

The authors concluded from these trials that nociceptive pain responds well to opioid therapy[3,49] and that neuropathic pain responds reasonably well, although slightly less favourably.[3,26,52,76] Patients with so-called idiopathic pain tend not to respond to opioids.[3,52,60] Patients tended to report favourable effects from opioids in the two studies that did not specify the diagnoses.[2,55]

Jadad has recently conducted a systematic review of randomized controlled clinical trials of opioids in neuropathic pain.[43] He identified nine trials that evaluated 104 patients in total. The trials had small sample sizes, heterogeneous patient populations, and designs. Some of the trials used fixed dose administration and, in some, the dose was titrated. However, he concluded that the best available evidence appears to support the contention that neuropathic pain can respond to opioids.

Table 2 shows the reported efficacy of opiates on different pain syndromes from prospective uncontrolled trials.[37] These studies reveal similar results to the RCT and, as expected, the positive effects from these trials are larger and more frequent than in the prospective controlled series.

A recent review of the limited literature regarding opioid efficacy in ischaemic pain has concluded that further research is needed before recommendations can be made.[66]

What are the arguments against using opioids long-term for chronic non-cancer pain?

Brena has argued that the needs of the chronic pain patient include not only reduction in subjective discomfort but also increase in general level of functioning, improvement in lifestyle, decrease in environmental stress and return to work. Whilst the first need may be met through opioid analgesia, he questions how well the other needs will be met.[9] Completion of a multidisciplinary pain rehabilitation

Table 2 Overall efficacy of opiates on different pain syndromes (prospective uncontrolled studies).[37] +=positive effect; –=no effect; +/–=mixed effects

Pain type	Reference	Results
Nociceptive	McQuay and colleagues[58]	+
Neuropathic	Fenollosa and colleagues[31]	+
	McQuay and colleagues[58]	+/–
	Urban and colleagues[96]	+
Idiopathic	McQuay and colleagues[58]	–
Not specified or mixed	Auld and colleagues[4]	+
	Gilmann and Lichtigfeld[36]	+
	Penn and Paice[64]	+
	Plummer and colleagues[67]	+/–

programme can result in a significant reduction in use and misuse of medications. This reduction can be associated with a decrease in pain intensity, an improved sense of well-being and an increase in physical activity, return to work and ability to manage pain and related problems.[9, 32]

Functional outcomes

Conflicting results have been obtained from studies investigating the effects of chronic opioid therapy on physical and psychological functioning.[2, 35, 39, 47, 60, 98] A reduction in pain intensity was accompanied by an improvement in the overall Pain Disability index (PDI) score and in most of the PDI sub-scales in one study comparing controlled-release codeine with placebo.[2] In a study of elderly patients with post-herpetic neuralgia, oxycodone reduced pain, allodynia, and disability scores compared with placebo.[98]

In contrast, although Moulin reported analgesic benefit from morphine, patients did not show any improvement in physical or psychological functioning.[60] Jamieson reported alleviation of pain and mood improvement, but no increase in activity levels in patients with chronic back pain. In this study, patients showed a preference for the short-acting opioid (oxycodone) as compared with the sustained-release morphine. They rated oxycodone as more helpful and reported being more confident in the knowledge that they had access to short-acting opioids should the pain flare up. Patients who varied their opioid dose from week to week reported less pain and better mood than those who did not. This runs counter to previous argument that taking opioid on a pain-contingent basis increases the likelihood of reinforcement of pain behaviour and dosage increase.[47]

Adverse outcomes

Organ toxicity

From clinical experience with the cancer pain population, the chronic non-cancer population and in the 'methadone-maintained' population, it would appear that long-term opioid therapy is not associated with major organ toxicity.[51, 89]

Effects on the immune system

There is an increasing body of evidence, obtained both from *in vitro* and *in vivo* studies in animals and humans, showing that exogenous opioids are able to suppress a variety of immunological responses.[15, 28, 61, 75] In humans, most data are based on the evaluation of immune function in i.v. heroin users and methadone-maintained patients (MMPs).[62, 74] However, effects have also been shown in human volunteers[99] and post-operative patients.[77] A recent study investigated immune responses in 10 patients with pain (seven non-malignant and three because of cancer) before and after treatment with sustained-release morphine and compared them with eight healthy control subjects not taking morphine. The cellular immune responses did not initially differ between patients and controls and did not show any significant changes during treatment. Immunoglobulin (Ig) production was reduced in the chronic pain patients before morphine was commenced and further reduced by morphine therapy. The clinical impact on the immune system as a whole of this suppression of humoral response remains to be elucidated.[63] It has been suggested that chronic opioid administration can induce a state of immune tolerance with normal resistance to viral infections.[12, 75]

It is apparent that this is an area in which a better understanding of these interactions has important clinical implications.

Pain facilitation

Hyperalgesia has been reported after systemic administration of high-dose morphine in cancer patients. There is some evidence that long-term use of opioids can induce a similar state of hyperexcitability of the central nervous system.[5] Current opioid use has been associated with decreased pain tolerance.[21]

Clinically, it has been recognized that some patients have an improvement in their pain after opioid reduction or withdrawal. The potential clinical ramifications of the effects of opioids on pain modulatory systems are important if they are to be increasingly prescribed to patients with a normal life expectancy.

Persistent side effects

Opioids produce clinically significant side effects, such as respiratory depression, sedation, cognitive impairment, nausea, itching, and constipation. In some patients, and especially in the elderly, adverse drug reactions can prevent the use of opioids.[49, 60] Whilst tolerance develops to many of these adverse effects, some remain and may be regarded as important in long-term use.

In a methadone maintenance programme, increased sweating was the most common side effect reported (48%). Constipation was also a common problem and all patients required daily laxatives in the first year. However, after 3 yr or more of methadone treatment, constipation was a persistent problem in only 17%. Insomnia and decreased libido and sexual functioning were also reported.[51]

Cognitive impairment

Cognitive impairment is a side effect that is potentially important with regard to long-term administration for non-malignant pain as this may affect driving, working ability, and may compromise engagement in a rehabilitation programme.

Early studies and case-reports have emphasized the negative effects of opioids, tranquillizers and sedatives/hypnotics in chronic pain patients, particularly with respect to cognitive functioning and personality.[54 56] Long-term use of tranquillizers appears to be associated with a greater risk of cognitive deficits compared with long-term opioid use.[40]

A recent comprehensive review has evaluated the available data on the effect of different opioids on a variety of psychomotor and cognitive tests in different populations (mainly volunteers and illicit opioid users).[101] Impairment by opioids tends to occur more often in healthy volunteers (who have little or no prior exposure to the drugs) than in those who have a history of opioid use. In general, for healthy volunteers, cognitive performance seems to be less impaired than psychomotor performance, for example, behaviour tends to 'slow down' rather than become more erratic.

For opioid-dependent users, laboratory studies show little if any cognitive impairment on multiple measures.[101] A recent study from Australia has shown cognitive deficits in MMP when compared with non-heroin-using controls. However, there was no correlation between the extent of impairment and methadone dosage and the researchers concluded that hypoxic brain damage from previous overdose, traumatic brain damage and alcohol-related brain damage amongst the MMPs were the three most important contributing factors.[25]

Pain itself has been shown to impair cognitive function and, therefore, studies performed to evaluate cognitive effects of opioids in pain-free controls cannot necessarily be extrapolated to patients in pain.[53] Pain may have an arousal effect and counter-act the sedative effects of opioids.

Continuous reaction time (CRT) is reduced in cancer patients on oral opioids compared with healthy controls.[85] Cancer patients with reduced performance status, in pain and on oral opioids have impaired neuropsychological functioning when compared with cancer patients with no pain and no disability. However, the use of long-term opioids *per se* does not affect any of the neuropsychological tests and pain itself appears to interfere with working memory more than oral opioid medication.[86] Bruera and colleagues demonstrated evidence of significant cognitive impairment in a group of patients who had recently had their opioid dose increased compared with those patients on a stable dose. Patient self-report indicated that patients themselves might be less aware of cognitive impairment than other opioid-induced side effects.[11]

In patients with non-cancer pain, no deterioration in cognitive function has been detected during long-acting opioid treatment and indeed an improvement on a measure of sustained attention and psychomotor speed was observed as pain intensity decreased during opioid usage.[39]

Driving

Vainio and colleagues specifically addressed the question of opioid-induced cognitive impairment in cancer patients in relation to driving. Psychomotor and neurological tests designed for professional drivers were conducted in two groups of cancer patients; one group was pain free and the other took regular oral morphine. There were no significant differences in most of the tests between the groups, although patients taking morphine did tend to show slower reactions, make more errors, and perform motor tasks more slowly. However, no differences existed in important functions related to driving, such as concentration and vigilance and mean performance levels in both groups were comparable with that of healthy volunteers.[97] They concluded that long-term stable opioid therapy does not affect psychomotor performance such that driving would be hazardous.

Most epidemiological studies suggest no increased risk of accidents (including road traffic accidents) and injuries amongst those who use opioids.[101] The relative risk of involvement in a road traffic accident for current users of any psychoactive drug has been reported as being 1.5 (95% confidence interval: 1.2–1.9). Regression analysis revealed that the type of psychoactive drug used was a factor: relative risk was not greater than 1 with oral opioid analgesics but was higher than 1 with benzodiazepines and antidepressants (e.g. amitriptyline).

Analysis of bodily fluids taken from fatally injured drivers in California and in Norway revealed that alcohol, cannabinoids, cocaine, and benzodiazepines were most frequently found. Samples rarely contained opioids.

Further studies on simulated and active driving are needed to gain a more comprehensive picture of the effects of opioids and of multiple medications on driving ability in patients with chronic non-cancer pain.

Clearly, patients should be warned to avoid activities like driving if they experience mental clouding and also about the possible additive effects of other centrally-acting drugs, such as alcohol or tricyclics.

Decision-making

Further studies are need to address whether chronic opioid therapy might impair decision-making in the work-place, although data so far suggest that this should not be so.

Elderly

There are important concerns about sedation and cognitive impairment in the elderly, especially in relation to falls. A review of 4500 patients with hip fracture compared with 24 041 hospitalized controls revealed an increased relative risk of fracture of 1.6 among those who were taking codeine or propoxyphene, especially if medication had been recently commenced.[83] Concurrent users of these opioids and psychotrophic drugs further increased their risk of hip fracture to 2.6 times that of non-users of either drug class.

Chronic pain is common in older people and often undertreated. Paracetamol may not provide adequate pain control. Chronic use of non-steroidal anti-inflammatory drugs is associated with a high frequency of adverse effects. Older people appear to be more sensitive to the analgesic effects of opioids as well as to the side effects. Low initial dosing of analgesics is required for all elderly patients with careful titration and monitoring and due recognition of a vulnerability to all opioid side effects.[1]

Table 3 Symptoms and signs of opioid withdrawal

Symptoms	Signs
Craving for opioids	Pupillary dilatation
Restlessness	Sweating
Irritability	Piloerection
Increased sensitivity to pain	Tachycardia
Nausea	Vomiting
Abdominal cramps	Diarrhoea
Myalgia	Hypertension
Dysphoria	Yawning
Insomnia	Fever
Anxiety	Rhinorrhoea

Tolerance

Tolerance refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect.[44]

Tolerance to the antinociceptive effects of opioids can be demonstrated in animal models and tolerance to the analgesic effects of opioids after acute and chronic dosing has been clearly shown in man.[17 42 57] Tolerance to the adverse effects of opioids also occurs and has positive benefit. There is a suggestion from animal research that ongoing nociception may modulate the development of tolerance to analgesic drugs. Many cancer patients with severe pain often have long periods of stable opioid dosage unless disease progression occurs.[10 20 34 81 95] Clinical surveys of long-term opioid use in patients with non-cancer pain, when an increasing nociceptive focus is unlikely, have not shown escalating drug dosage to be an inevitable clinical problem, although some dose increase is often observed over time.[31 35 64 67 90 96 100 102]

Management of tolerance

Clinicians must evolve strategies for managing increasing analgesic dose and possible tolerance in the patient with non-cancer pain. Principles that have been effective in the management of tolerance in the cancer patient would seem appropriate: (1) the 'differential diagnosis' for declining analgesic effectiveness should be considered and treated,[70] (2) the dose of opioid can be increased, (3) an alternative opioid can be substituted at a reduced dose, and (4) alternative pain management strategies can be introduced with dose stabilization or reduction.

Physical dependence

This has been defined as 'the potential for an abstinence syndrome, or withdrawal, following abrupt dose reduction, discontinuation of the drug or administration of an antagonist drug'.[44] Symptoms and signs of withdrawal are described in Table 3.

Physical dependence should be assumed to exist if opioids have been given repeatedly for a few days. However, 55% of arthritis patients prescribed long-term opioids reported that they did not take their medication on a daily basis because of fear of dependence and addiction. Withdrawal symptoms were not spontaneously reported.[100] Although, with regular opioid medications, overt withdrawal is unlikely, it has been postulated that subtle episodic withdrawal symptoms may increase baseline pain and associated problems such as mood and sleep disturbance. This might explain the improvement reported by some patients when short-acting opioids are reduced and eliminated or replaced with long-acting medications.[79]

In cancer patients, withdrawal symptoms do not appear to be problematic provided opioids are withdrawn slowly[81] and, if they do occur, they can be controlled by resumption of a small dose of opioid.[95] Withdrawal symptoms do not appear to be a barrier to opioid reduction in non-cancer patients within the setting of a pain management programme.[13 72]

Addiction

Studies in the 1920s and 1950s were influential in supporting the notion that chronic opioid therapy leads to addiction. Between 9 and 27% of addicts reported that their first exposure to opioids was as a result of a therapeutic prescription for pain.[50 73] However, these studies have methodological flaws and more recent reports have suggested that the risk of iatrogenic opioid addiction is very low.[65 71]

Addiction is a complex phenomenon, with several components: genetic, environmental, psychological and the inherent properties of the drug itself. Current evidence suggests that the development of addiction is a result of, in part, to neurochemical stimulation of reward centres in the limbic system and related areas of the brain. Most addiction specialists agree that the alcoholic, or other drug-addicted individuals should be viewed as being at risk for addiction to substances other than their drug of choice.[78] The course of addictive disease may be variable from individual to individual and an addictive pattern of drug use may occur at any time because of a combination of factors. With treatment and/or abstinence, the individual may recover. Nevertheless, the disease of addiction, once evolved, is conceptionalized by most addicitonists as incurable.

Table 4 American Society of Addiction Medicine definitions related to the use of opioids in pain treatment[22]

Physical dependence
Physical dependence on an opioid is a physiological state in which abrupt cessation of the opioid or administration of an opioid antagonist, results in withdrawal syndrome. Physical dependency on opioids is an expected occurrence in all individuals in the presence of continuous use of opioids for therapeutic or non-therapeutic purposes. It does not, in and of itself, imply addiction.

Tolerance
Tolerance is a form of neuroadaptation to the effects of chronically administered opioids (or other medicines), which is indicated by the need for increasing or more frequent doses to achieve the initial effects of the drug. Tolerance may occur to both the analgesic effects of opioids and to unwanted side effects such as respiratory depression, sedation, or nausea. The occurrence of tolerance is variable in occurrence, but it does not, in and of itself, imply addiction.

Addiction
Addiction in the context of pain treatment with opioids is characterized by a persistent pattern of dysfunctional opioid use that may involve any or all of the following:
- adverse consequences associated with the use of opioids;
- loss of control over the use of opioids;
- preoccupation with obtaining opioids despite the presence of adequate analgesia.

Prevalence

Current estimates from North America indicate that between 3 and 19% of chronic pain patients suffer an addictive disorder, which parallels the lifetime prevalence rates of addictive disease in the general population (3–16%).[33] A recent Swedish study of 414 patients referred to a chronic pain centre and indicated a higher prevalence (23.4%), with 9.4% additionally meeting diagnostic criteria for substance use disorder in remission. Current dependency was most common for analgesics (12.6%), alcohol (9.7%), and sedatives (7.0%).[41]

Savage has identified reasons why the incidence of addiction may be higher in patients with chronic pain compared with the non-pain population.[78] First, traumatic injury is often the initiating factors in the development of chronic pain and there is a relatively high incidence of alcoholism amongst individuals who sustain trauma. One study found that 49% of individuals with spinal cord injury screened positive for alcoholism. Alcohol is thought to be a factor in over 50% of road traffic accidents. Second, some studies have suggested an association between childhood sexual or physical abuse and the development of chronic pain. Physical and sexual abuse occurs more commonly in families in which one or more parent is alcoholic. If the children of alcoholics are over-represented in pain clinics for whatever reason, then it should follow that addictive disease will be more common, as the children of alcoholics are more likely to develop alcoholism and other addictive disease. Third, there is accumulating evidence regarding interrelationships between the neurophysiological pathways that mediate pain and those that mediate addiction. Fourth, chemical dependency itself may sustain the pain. Lastly, addicted individuals often cannot fulfil their usual work and domestic roles, suffer financial losses and relationship problems and may develop secondary physical complaints. This may feed into a chronic pain-distress/impairment cycle.

Identification

Alcoholism and other addictions are underdiagnosed in a medical setting. Common reasons for underdiagnosis include:

1. Lack of skill in recognition on the part of the doctor.
2. Uneasiness about discussing drugs and alcohol.
3. Unfamiliarity about resources available for treatment.
4. Belief that the condition is untreatable.
5. Belief that the condition is moral rather than medical.
6. Belief that the addiction is secondary to the pain with the expectation that it will resolve when the pain is successfully treated.
7. Belief that it is a totally independent problem and, therefore, not of concern of the doctor in the pain clinic.

Experience suggests that pain in patients with addictive disease does not improve unless their addiction is also treated.[32]

The clinician should make some conscious effort to identify the alcoholic or addict in the pain management clinic. History, physical examination, and laboratory studies (including elevated GGT and MCV) may be helpful.

Several short screening tests for alcoholism have been developed such as the CAGE questionnaire. (C=Have you ever felt you ought to Cut down on your drinking? A=Have people ever Annoyed you by criticizing your drinking? G=have you ever felt Guilty about your drinking? E=Have you ever had an 'Eye-opener' first thing in the morning to steady your nerves or get rid of a hangover?). Equally important is identifying the individual who is in recovery. All individuals in recovery are at lifetime risk of relapse. Many addiction specialists recommend avoidance of all potentially intoxicating or dependency producing medications. Involvement of a specialist in addiction medicine may be appropriate if features of addiction are present on initial examination.[32 82]

The American Society of Addiction Medicine has recognized the limitations of the DSM-IV criteria for diagnosing addiction in chronic pain patients treated with opioids. Separate recommendations for defining addiction in this group have been developed and are shown in Table 4.[22]

Addiction in the context of pain treatment with opioids is characterized by a persistent pattern of dysfunctional opioid use that may involve any or all of the following:

- adverse consequences associated with the use of opioids;

- loss of control over the use of opioids;
- pre-occupation with obtaining opioids despite the presence of adequate analgesia.

'Prescription opiate abuse'

'Prescription opiate abuse' has been used to define misuse of prescribed opiate medications by patients in the clinical setting who are being treated by a physician for a recognized pain condition.[16] A set of behaviours that suggested, or were consistent with, opiate abuse was formulated and patients attending the pain clinic were assessed according to these criteria.

A patient qualified as a 'prescription opiate abuser' if they met three or more of the following criteria.

(a) Patient displays an overwhelming focus on opiate issues during pain clinic visits that occupy a significant proportion of the visit and impede progress with other issues regarding the patient's pain. This behaviour must persist beyond the third clinic treatment session.

(b) The patient has a pattern of early prescriptions (three or more) or escalating drug use in the absence of acute change in his/her medical condition.

(c) The patient generates multiple telephone calls or unscheduled visits to request more opiates, early prescriptions or problems associated with opiate prescription. A patient may qualify with fewer visits if he/she creates a disturbance with the office staff.

(d) There is a pattern of prescription problems for a variety of reasons that may include lost, spilled or stolen medications.

(e) The patient has supplemental sources of opiates obtained from multiple providers, emergency departments or illegal sources.

Seventy-six out of 403 pain clinic patients, who were using opioids for longer than 6 months, were rated independently against the above criteria by two physicians. Twenty-one (27.6%) met three or more of the five possible criteria for prescription opiate abuse.[16] 'Drug-seeking' behaviour, particularly surrounding prescriptions, would seem to be 'relatively more predictive' of addiction.[16 22 69] Family members and the patients themselves may also have insight into whether the patient is addicted.[22]

Previous history of addictive disease

There are conflicting data concerning a previous history of drug abuse or alcoholism. Some studies have shown no differences between the abusers and non-abusers for a history of previous drug or alcohol abuse.[16 100] In other studies, a previous history of addictive disease has been positively associated with prescription drug misuse.[22] As there is no proven method for identifying patients at risk of addiction, this must be viewed as a potential risk.

Diversion and non-medical use

All opioids have a street value and may be traded or sold. This applies to weak opioids such as dihydrocodeine as well as to strong opioids, and to long-acting as well as short-acting formulations. Currently, in Leicester, one MST 30 mg tablet costs £3.00 'on the street' (personal communication).

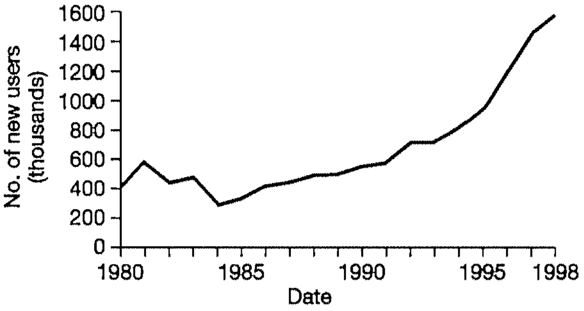

Fig 1 Annual numbers of new users of pain relievers non-medically 1990–1998. Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, National Household Survey on Drug Abuse, 1999.

The 1999 National Household Survey on Drug Abuse (NHSDA) released by the Substance Abuse and Mental Health Services Administration indicated there were 2.6 million Americans reporting analgesic use for non-medical reasons. An estimated 1.6 million people used prescription analgesics non-medically for the first time in 1998, representing a significant increase since 1990 when there were 564 000 initiates (Fig. 1).

Physicians need to be aware that drugs they prescribe may be diverted. They have a responsibility to perform a thorough assessment of risk factors and to develop practices to ensure that their patients are taking medication as prescribed. A single prescriber is advisable. Close liaison with the General Practitioner is essential as they may be better informed of aberrant behaviour than the hospital specialist. However, physicians should not withhold opioids from an individual patient requiring strong analgesics because of general concerns regarding diversion.

Guidelines

It would appear that there is a consensus view that a subset of patients with chronic non-malignant pain may have less pain and function better if treated with opioids.[29 46 69 80] Critical questions which must be addressed to ensure the maximum benefit for the prescription of opioids for chronic non-malignant pain are as follows.

- Who are appropriate patients?
- Who are appropriate prescribing doctors?
- How should opioids be initially prescribed?
- Which opioids?
- Informed consent.
- What are appropriate outcome measures?
- Review.
- How and when should the opioids be withdrawn?

Guidelines have been proposed to assist practitioners to identify those patients who are suitable for chronic opioid therapy and to suggest how they may best be managed.[14 38 59 69 80 94 102] In May 1998, the Federation of State Medical Boards of the United States, Inc. released a policy document entitled 'Model guidelines for the use of controlled substances for the treatment of pain' and this is available on the internet at: (http://www.medsch.wisc.edu/painpolicy/domestic/model.htm).

There are common elements to many of these guidelines, which may be summarized as follows.

Evaluation of the patient

The doctor should perform a thorough history and examination of the patient. This should include a pain diagnosis, including an estimate of nociceptive, neuropathic and psychosocial contributions, current and past treatments, functional impairment, and history of substance abuse.

There is general agreement that opioids for non-cancer pain should only be prescribed after all other reasonable attempts at analgesia have failed and should be a part of a comprehensive treatment approach. Patients with a past history of substance abuse should not necessarily be denied a trial of opioid therapy, but will require more careful prescribing and follow-up. It has been suggested that either an i.v. or spinal opioid challenge should be administered to assess opioid-responsiveness. Whilst this may aid decision-making in difficult cases, for most patients, low-dose oral opioids with gradual dose titration will suffice.

Treatment plan

The primary purpose of long-term opioid therapy should be improved quality of life for the patient. The patient and clinician need to negotiate an individualized treatment plan to find the optimum balance of pain relief, functional improvement, and side effects. Emphasis should be placed on capitalizing on improved analgesia by an increase in physical and psychosocial functioning.

An initial trial of therapy with goals and an end-point agreed between the physician and patient should precede any decision with regard to long-term treatment. Failure to achieve partial analgesia with incremental dose increases may indicate a non-responsive pain syndrome. A single clinician should take primary responsibility for drug prescribing, at least in the early stages of treatment.

Most of the guidelines suggest the use of a long-acting opioid preparation on a time-contingent basis. The rationale for this is that more stable concentrations of drug in the blood can be attained, thereby allowing better tolerance to side effects and a reduction in the possible reinforcement of pain behaviour that can occur when analgesics are taken on a pain-contingent basis. However, chronic pain patients are a heterogeneous group and some patients with low back pain have shown a preference for short-acting medication, with no evidence of inevitable dose escalation.[47] Injectable opioids should not be used to treat chronic non-cancer pain.[6 30] In particular, i.m. pethidine should be avoided. It has a short half-life and the potential for excitatory central nervous system toxicity from accumulated norpethidine concentrations after repeated doses.

Informed consent

Physicians should discuss the risks and benefits of opioid therapy. Points to be covered should include likelihood of physical dependence, potential for cognitive impairment, particularly after dose increase or if taken with other sedative drugs, and recognition of the risk of addictive behaviour. Some guidelines suggest written contracts for patients at high risk of non-compliance.

Periodic review

Ongoing assessment is an essential part of the management of the patient with opioid therapy and should take place at reasonable intervals based on the individual circumstances of the patient.

In evaluating the efficacy of opioid therapy, it is recommended that the following points be covered:

- patient's self-report of pain;
- level of physical and psychological functioning;
- side effects of opioid therapy;
- any suspicious drug-seeking or aberrant behaviours;.
- any changes in drug dosage to be recorded and the reasons for them;
- correct procedures to be followed for writing prescriptions.

Dose escalation needs to be comprehensively assessed and managed according to cause. The adverse effects of opioid therapy may sometimes lead to a persistent decrease in function. In some cases, a gradual reduction in dose—possibly leading to discontinuation of therapy—may be indicated. Information from family members and friends may be helpful.

Consultation

Referral to other specialists, such as a Consultant Psychiatrist with expertise in addiction medicine, should be considered for those patients who develop symptoms of drug misuse.

Documentation

Documentation is essential to demonstrate the evaluation process, the rationale for long-term opioids in the context of the overall management plan, informed consent and periodic review of the status of the patient.

No empirical studies have been conducted to substantiate these guidelines. If guidelines are to be widely accepted, they must be applicable to the range of patients that present with severe intractable pain. Patients that might be considered for opioid therapy may have a wide range of diagnoses and may be treated in a variety of settings, for example, primary care, rheumatology, neurology, and pain management clinics. Patients in pain management clinics and especially pain management programmes may have a high rate of psychopathology, abnormal pain behaviours, abnormal family, social and work situations and disability factors that may make treatment with opioids more difficult.

The currently available guidelines all suffer from a local cultural and legal bias depending on their country of origin. A case has been made for specific guidelines for use in the UK to be researched and formulated.

Clearly, the treatment goals in chronic non-malignant pain are a reduction of symptoms and suffering as well as functional improvement, decreased dependence on the health care system and return to work and social functioning. Analgesics are only part of this treatment. There may be a population of patients who clearly benefit from opioids and we need to identify who they are and how they can best be managed.

References

1 Anonymous. The Management of chronic pain in older persons [Clinical Practice Guidelines]. *J Am Geriatr Soc* 1998; **46**: 635–51

2 Arkinstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke A. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain* 1995; **62**: 169–78

3 Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 1988; **33**: 11–23

4 Auld AW, Maki-Jokela A, Murdoch DM. Intraspinal narcotic analgesia in the treatment of chronic pain. *Spine* 1985; **10**: 777–81

5 Basbaum AI. Insights into the development of tolerance. *Pain* 1995; **61**: 349–52

6 Bell JR. Australian trends in opioid prescribing for non-cancer pain, 1986–1996. *Med J Aust* 1997; **167**: 26–9

7 Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Ann Clin Psychiatry* 1992; **4**: 185–92

8 Bowsher D, Rigge M, Sopp L. Prevalence of chronic pain in the British population: a telephone survey of 1037 households. *Pain Clin* 1991; **4**: 223–31

9 Brena SF, Sanders SH. Opioids in nonmalignant pain: questions in search of answers. *Clin J Pain* 1991; **7**: 342–5

10 Bresda FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. *J Clinl Oncol* 1992; **10**: 149–55

11 Breura E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989; **39**: 13–16

12 Bryant HU, Bernton EW, Holaday JW. Morphine-induced immunomodulation in mice: temporal relationships. *J Pharmacol Exp Ther* 1988; **245**: 913–20

13 Buckley FP, Sizemore WA, Charlton JE. Medication management in patients with chronic non-malignant pain. A review of the use of a drug withdrawal protocol. *Pain* 1986; **26**: 153–65

14 Canadian Pain Society. Use of opioid analgesics for the treatment of chronic noncancer pain—A consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 1998; **3**: 197–208

15 Carr DJ, Rogers TJ, Weber RJ. The relevance of opioids and opioid receptors on immunocompetence and immune homeostasis. *Proc Soc Exp Biol Med* 1996; **213**: 248–57

16 Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain* 1997; **13**: 150–5

17 Chapman CR, Hill HF. Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit. *Cancer* 1989; **63**: 1636–4

18 Clark HW, Sees KL. Opioids, chronic pain, and the law. *J Pain Symp Manage* 1993; **8**: 297–305

19 Clinical Standards Advisory Group 'Services for Patients with Pain'. London: Department of Health, 2000

20 Collin E, Poulain P, Gauvin-Piquard A, Petit G, Pichard-Leandri. E. Is disease progression the major factor in morphine 'tolerance' in cancer pain treatment? *Pain* 1993; **55**: 319–26

21 Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. *J Pain Symptom Manage* 1994; **9**: 462–73

22 Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and 'problematic' substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage* 1998; **16**: 355–63

23 Coniam SW. Prescribing opioids for chronic pain in non-malignant disease. In: Tywcross RG, ed. *The Edinburgh Symposium on Pain Control and Medical Education. Royal Society of Medicine International Congress and Symposium Series*. London: Royal Society of Medicine, 1989; **149**: 205–10

24 Crombie IK. Epidemiology of persistent pain. In: Jensen TS, Turner JA, Wiesenfeld-Hallin Z, eds. *Proceedings of the 8th World Congress on Pain*. Seattle: IASP Press, 1997; 53–61

25 Darke S, Sims J, McDonald, Wickes W. Cognitive impairment among methadone maintenance patients. *Addiction* 2000; **95**: 687–95

26 Dellemijin PL, Vanneste JAL. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. *Lancet* 1997; **349**: 753–8

27 Elliot AM, Smith BH. Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999; **354**: 1248–52

28 Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol* 1998; **83**: 36–44

29 Evans PJD. Opioids for chronic musculoskeletal pain. In: Kalso E, McQuay HJ, Wiesenfeld-Hallin Z, eds. *Opioid Sensitivity of Chronic Noncancer Pain*. IASP Press, 1999; 349–65

30 Evans PJD. Narcotic addiction in patients with chronic pain. *Anaesthesia* 1981; **36**: 597–602

31 Fenollosa P, Pallares J, Cervera J, Pelegrin F, Inigo V, Giner M, Forner V. Chronic pain in the spinal cord injured: statistical approach and pharmacological treatment. *Paraplegia* 1993; **31**: 722–9

32 Finlayson RE, Maruta T, Morse RM, Martin MA. Substance dependence and chronic pain: experience with treatment and follow-up results. *Pain* 1986; **26**: 175–80

33 Fishbain DA, Rosomoff, HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain* 1992; **8**: 77–85

34 Foley KM. Clinical tolerance to opioids. In: Basbaum AI, Besson J-M.

Towards A New Pharmacotherapy Of Pain. John Wiley & Sons Ltd, 1991; 181–203

35 France RD, Urban BJ, Keefe FJ. Long-term use of narcotic analgesics in chronic pain. *Soc Sci Med* 1984; **19**: 1379–82

36 Gilmann MA, Lichtigfeld FJ. A comparison of the effects of morphine sulphate and nitrous oxide analgesia on chronic pain states in man. *J Neurological Sci* 1981; **49**: 41–45

37 Graven S, de Vet HCW, van Kleefe M, Weber WEJ. Opioids in chronic non-malignant pain: a criteria-based review of the literature. In: Devor M, Rowbotham MC, Wiesenfeld-Hallin Z, eds. *Proceedings of the 9th World Congress on Pain. Progress in Pain Research and Management Volume 16.* Seattle: IASP Press, 2000; 965–72

38 Graziotti PJ, Gourcke CR. The use of oral opioids in patients with chronic non-cancer pain *Med J Aust* 1997; **167**: 30–4

39 Haythornthwaite JA, Menefee, LA, Quatrano-Piacentini, Papagallo M. Outcome of chronic opioid therapy for non-cancer pain. *J Pain Symptom Manage* 1998; **15**: 185–93

40 Hendler N, Cimini C, Ma T, Long D. A comparison of cognitive impairment due to benzodiazepines and to narcotics. *Am J Psychiatry* 1980; **137**: 828–30

41 Hoffman NG, Olofsson O, Salen B, Wickstrom L. Prevalence of abuse and dependency in chronic pain patients. *Int J Addictions* 1995; **30**: 919–27

42 Houde RW. The analgesic connection: the Nathan B. Eddy memorial lecture. In: Harris LS, ed. *Problems of Drug Dependence 1984, Proceedings of the 46th Annual Scientific Meeting, The Committee on Problems of Drug Dependence.* NIDA Research Monograph 1985; **55**: 4–13

43 Jadad AR. Opioids in the treatment of neuropathic pain: A systematic review of controlled clinical trials. In: Bruera E, Portenoy RK, eds. *Topics in Palliative Care.* New York: Oxford University Press, 1998; 31–40

44 Jaffe JH. Drug addiction and drug abuse. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*, 7th edn. New York: Macmillan, 1985; 532–581

45 Jamieson RN, Anderson KO, Peeters-Asdourian C, Ferrante FM. Survey of opioid use in chronic nonmalignant pain patients. *Reg Anaesth* 1994; **19**: 225–30

46 Jamieson RN. Comprehensive pretreatment and outcome assessment for chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage* 1996; **11**: 231–41

47 Jamieson RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomised prospective study. *Spine* 1998; **23**: 2591–600

48 Joranson DE, Gilson AM. Controlled substances, medical practice, and the law. In: Schwartz HI, ed. *Psychiatric Practice Under Fire: The Influence of Government, the Media and Special Interests on Somatic Therapies.* Washington, DC: American Psychiatric Press, Inc., 1994; 173–194

49 Kjaersgaard-Andersen P, Nafei A, Skov O, Madsen F, Andersen HM, Kroner K, Hvass I, Gjodereum O, Pedersen L, Branebjerg PE. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. *Pain* 1990; **43**: 303–18

50 Kolb L. Types and characteristics of drug addicts. *Mental Hygiene* 1925; **9**: 300

51 Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. *JAMA* 1973; **223**: 665–8

52 Kupers RC, Konings H, Adriaensen H, Gybels JM. Morphine differentially affects the sensory and affective pain ratings in neuropathic and idiopathic forms of pain. *Pain* 1991; **47**: 5–12

53 Lorenz J, Beck H, Bromm B. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. *Pain* 1997; **73**: 369–75

54 Maruta T. Prescription drug-induced organic brain syndrome. *Am J Psychiatry* 1978; **135**: 376–7

55 Mays KS, Lipmann JJ, Schnapp M. Local analgesia without anaesthesia using peripheral perineural morphine injections. *Anaesth Analg* 1987; **66**: 417–20

56 McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. *Pain* 1984; **18**: 169–77

57 McQuay HJ, Bullingham RES, Moore RA. Acute opiate tolerance in man. *Life Sci* 1981; **28**: 2513–7

58 McQuay H, Jadad AR, Carroll D, Faura C, Glynn CJ, Moore RA, Liu Y. Opioid sensitivity of chronic pain: a patient-controlled analgesia method. *Anaesthesia* 1992; **47**: 757–67

59 Merry AF, Schug SA, Richards EG, Large RG. Opioids in chronic pain of non malignant origin: state of the debate in New Zealand. *Eur J Pain* 1992; **13**: 39–43

60 Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Mersky H. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996; **347**: 143–7

61 Nelson CJ, Dykstra LA, Lysle DT. Comparison of the time course of morphine's analgesic and immunologic effects. *Anesth Analg* 1997; **85**: 620–6

62 Novick DM, Ochshorn M, Ghali V, Croxson TS, Mercer WD, Chiorazzi N, Kreek MJ. Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. *J Pharmacol Exp Ther* 1989; **250**: 606–10

63 Palm S, Lehzen S, Mignat C, Steinmann J, Leimenstoll G, Maier C. Does prolonged oral treatment with sustained-release morphine tablets alter immune function? *Anesth Analg* 1998; **86**: 166–72

64 Penn RD, Paice JA. Chronic intrathecal morphine for intractable pain. *J Neurosurg* 1987; **67**: 182–6

65 Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. *Pain* 1982; **13**: 267–80

66 Persson J. Opioids in ischaemic pain. In: Kalso E, McQuay H, Wiesenfeld-Hallin Z, eds. *Opioid Sensitivity of Chronic Noncancer pain. Progress in Pain Research and Mechanisms, Volume 14.* Seattle: IASP Press, 1999; 337–47

67 Plummer JL, Cherry DA, Cousins MJ, Gourlay GK, Onley MM, Evans KHA. Long-term spinal administration of morphine in cancer and non-cancer pain: a retrospective study. *Pain* 1991; **44**: 215–20

68 Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; **25**: 171–86

69 Portenoy RK Opioid therapy for chronic nonmalignant pain: A review of the critical issues. *J Pain Symptom Manage* 1996; **11**: 203–17

70 Portenoy RK. Tolerance to opioid analgesics: clinical aspects. *Cancer Surv* 1994; **21**: 49–65

71 Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med* 1980; **302**: 123

72 Ralphs JA, C de C Williams, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. *Pain* 1994; **56**: 279–88

73 Rayport M. Experience in the management of patients medically addicted to narcotics. *JAMA* 1954; **165**: 684–91

74 Risdahl JM, Khanna KV, Peterson PK, Molitor TW. Opiates and infection. *J Neuroimmunol* 1998; **83**: 4–18

75 Rouveix B. Opiates and immune function. Consequences on infectious diseases with special references for AIDS. *Therapie* 1992; **47**: 503–12

76 Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of post-herpetic neuralgia. *Neurology* 1991; **41**: 1024–8

77 Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai A. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg* 2000; **90**: 1411–4

78 Savage SR. Addiction in the treatment of pain: significance, recognition and management. *J Pain Symptom Manage* 1993; **8**: 265–77

79 Savage SR. Long-term opioid therapy: assessment of consequences and risks. *J Pain Symptom Manage* 1996; **11**: 274–86

80 Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. *J Pain Symptom Manage* 1993; **8**: 279–88

81 Schug SA, Zech D, Grond S, Jung H, Meuser T, Stobbe B. A long-term survey of morphine in cancer pain patients. *J Pain Symptom Manage* 1992; **7**: 259–66

82 Sees KL, Clark HW. Opioid use in the treatment of chronic pain: assessment of addiction. *J Pain Symptom Manage* 1993; **8**: 257–64

83 Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol* 1992; **47**: M111–5

84 Simpson RK, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. *J Pain Symptom Manage* 1997; **14**: 218–24

85 Sjorgren P, Banning A. Pain, sedation and reaction time during long-term treatment of cancer patients with oral and epidural opioids. *Pain* 1989; **39**: 5–11

86 Sjogren P, Olsen AK, Thomsen AB, Dalberg J. Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. *Pain* 2000; **86**: 237–45

87 Somerville MA. Opioids for chronic pain of non-malignant origin—coercion or consent? *Health Care Anal* 1995; **3**: 12–14

88 Sorenson HT, Rasmussen HH, Moller-Petersen JF, Ejlersen E, Hamburger H, Olesen F. Epidemiology of pain requiring strong analgesics outside hospital in a geographically defined population in Denmark. *Danish Med Bull* 1992; **39**: 464–7

89 Taub A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata LM, Collins JG, eds. *Narcotic Analgesics in Anesthesiology*. Baltimore/London: Williams & Wilkins, 1982; 199–208

90 Tennant F, Robinson D, Sagherian A, Seecof R. Chronic opioid treatment of intractable, non-malignant pain. *NIDA Res Monogr* 1998; **81**: 174–80

91 Turk DC, Brody MC, Okifuji EA. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain* 1994; **59**: 201–8

92 Turk DC, Brody MC. What position do APS's physicians take on chronic opioid therapy? *Am Pain Soc Bull* 1992; **2**: 1–5

93 Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain* 1997; **13**: 330–6

94 Turk DC. Clinicians attitudes about prolonged use of opioids and the issue of patient heterogeneity. *J Pain Symptom Manage* 1996; **11**: 218–30

95 Twycross RG. Clinical experience with diamorphone in advanced malignant disease. *Int J Clin Pharmacol* 1974; **9**: 184–98

96 Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. *Pain* 1986; **24**: 191–6

97 Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995; **346**: 667–70

98 Watson CP, Babul N. A randomized trial in postherpetic neuralgia. *Neurology* 1998; **50**: 1837–41

99 Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, Guyre PM. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 1995; **83**: 500–8

100 Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. *Arthrit Rheuma* 1998; **41**: 1603–12

101 Zacny JP. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *J Exp Clin Psychopharmacol* 1995; **3**: 432–66

102 Zenz M, Strumpf, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage* 1992; **7**: 69–77

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Role of psychology in pain management

C. Eccleston

Pain Management Unit, University of Bath, Bath BA2 7AY, UK

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'I went to see someone, I can't remember his name, a Mr somebody, who told me that my spine was crumbling. Well obviously I have to be careful not to bend in case I make it worse, or it snaps!'

Patients often report what may seem to the health-care professional to be bizarre or irrational beliefs. However, when we investigate further the background of these beliefs they can often have a simple, if important, route. The above statement, for example, was spoken in clinic by a chronic back pain patient who had been informed that he had marked 'disc degeneration' on x-ray findings. For all patients with pain, what is understood about the meaning of pain, disease and/or disability will play a part in the presentation of the problem and the effectiveness of treatment. For patients with chronic pain, these beliefs form part of the psychosocial context, known to be the largest influence in predicting the extent of pain-associated disability. For the clinician interested in improving assessment and treatment, an understanding of the role of psychological factors in the presentation of a pain problem is a fundamental requirement.

In this article I will introduce the field of psychology as applied to pain management and attempt to demystify some of the practices and translate some of the jargon. First, I will introduce the relevant psychological theory, focusing on the clinical utility of the research findings. Secondly, I will expand on the psychology of the chronic pain patient. Finally, I will present the evidence for psychologically orientated therapies for chronic pain management.

Psychological factors in pain perception

The importance of psychology in the expression, understanding and treatment of pain was recognized in early theories of nociception. These theories accepted the top-down influence of midbrain and cortical structures in pain expression.[36] Similarly, with the advancement of the psychology of behaviour in the 1950s and 1960s, the role of environment in shaping treatment behaviour and complaining behaviour was also further developed.[19] These theories were clinical in nature as they arose from the growing problem of patients suffering from chronic unremitting pain and disability. Psychology also found its place in pain treatments after the growing recognition that the extent of complaint and disability reported by many patients could not be explained by the extent of damage or disease.[20 21]

Pain, tissue damage and disability

Pain is the most common reason for patients to enter health-care settings and the most common reason given for self-medication.[61] Pain interrupts all other activity and arrests current behaviour. It functions to prime escape or protective behaviour.[15] As it is an everyday and frequent experience, there is also a common understanding of pain, both lay and professional, that it is a useful signal of damage.[1] Indeed, in the majority of cases pain is a relatively reliable signal of damage and one that refers well to its spatial location. Also, the intensity of pain often refers well to the extent of damage. For example, extracting two teeth hurts about twice as much as extracting one tooth.[28]

There is, however, a number of cases where the extent of damage does not refer well to the experience of pain.[65] For example, some people report pain that has no identifiable lesion, as in many cases of back pain, headache and angina. It is also possible to have tissue damage without any pain. For example, up to 40% of patients with established reversible myocardial ischaemia do not report pain. More recently, it has been recognized that it is possible to experience pain in a location distal to the damage or to experience pain in a missing or extra limb or location. Even under laboratory conditions, where we can control the intensity of the pain-inducing stimulus, there is a great deal of variability in patient response.[12] We should be mindful of the fact that pain is not a reliable indicator of tissue damage and that tissue damage is not a reliable indicator of pain.

There is also a number of cases where the extent of damage and the extent of pain together do not refer well to the experience of disability. Some patients appear not to be disabled by extensive damage and pain, whereas other patients respond with extensive disability to seemingly minor damage and pain. This variability can be witnessed in everyday practice. Anyone who is in the business of hurting people as part of their routine work will understand that different people respond differently to the same procedure

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under the same circumstances, and that the same people respond to the same procedure differently at different times or under different circumstances. A brief and unscientific survey of colleagues or friends as to their choice of analgesia during dental procedures will quickly exemplify this variability.

Understanding differential responding

We can successfully conclude that people are different and respond differently to pain-inducing stimuli and to attempts at pain management. This is perhaps not the most astounding and revelatory of claims ever made but it can be of crucial importance for the delivery of successful pain management. If we can understand what predicts these differences we may be able to improve treatment delivery and effectiveness.

Early theories of the psychology of pain assessed global factors such as personality, gender, age and culture. These global or broad-sweep explanations seem to have an intuitive appeal and one still hears them supported in everyday practice. The evidence in support of these explanations, however, is not always persuasive or conclusive.

Personality

A number of studies have attempted to describe or uncover what may be thought of as a pain-prone personality. It was thought that those who were less hardy or less robust to the hardships of the world would show less tolerance of pain stimuli and would be more complaining of pain. In addition, there was also the idea that the pain expressed by patients was a manifestation of guilt or of loss, or that pain revealed a self-destructive, sadomasochistic style of sexual development.[16] There is no evidence, however, to support these ideas. I mean not to negate the importance of differences in individual personalities, but rather that the search for a unified pain personality was unsuccessful. The experience of pain does not prevent personality disorders but neither is it thought to be a mask or alternative manifestation of them.[67]

Gender

In an excellent recent review of this field, Anita Unruh reported that 'In most studies, women report more severe levels of pain, more frequent pain and pain of longer duration than do men.'[59] Women are more likely to experience recurrent pain, have moderate and severe pain from menstruation and childbirth and may be at increased risk of disability arising from pain. Unruh also reported that, despite the fact that women report more pain than men, women are at greater risk of being labelled as having a psychogenic disorder and are more vulnerable to pain being explained as a purely psychological (used pejoratively in this case to mean unreal) phenomenon.

Age

Very little is known about the specific effects of age and ageing and about the psychology of pain for specific age groups. For example, effective pain management in children has been hampered by the erroneous beliefs that neonates and infants could not feel pain and that children would respond addictively to opioid analgesia. We now know these ideas to be without support.[22] An important but unresearched area is the effects of emotional and cognitive development upon the experience of pain for children and adolescents. At the other end of the lifespan, we are also only now beginning to learn about the effects of cognitive impairment on pain experience.[41]

Culture

Early studies of the effect of culture focused upon the reports of ethnic differences in pain expression. However, the study of culture extends further than the ethnic group membership of patients. For example, a recent interesting study showed that ethnic differences (in a US sample) did not affect the report of post-operative pain or patient-controlled analgesia for post-operative pain, but did, however, affect physician prescribing behaviour.[40] More recently, the study of cultural influences has extended to the broader study of the cultural construction of pain and has started to embrace the use of anthropological and sociological methods.[39]

Specific psychological factors

Although early theories focused on global factors, more recent areas of study have developed our understanding of specific psychological traits or specific states of experience that affect the report of pain and suffering.

Fear

Pain functions to threaten danger and invoke an escape or ameliorative response. This threat component of pain is not an addition to the sensory component, nor does it follow from the sensory aspects. Instead, it is a primary and central component as it urges analgesic behaviour. Fear and anxiety processes have been studied from a number of perspectives, although they cover essentially the same issue. The most relevant to clinical practice are reviewed here.

Attention and vigilance

Threatening pain is a stimulus that orients attention to both the source of pain and the potential for escape or analgesia. Some people have increased or heightened attention to pain sensation. In particular, where the threat of pain is constant or recurrent, a pattern of vigilance to pain can develop. McCracken developed a measure of vigilance to pain with a sample of chronic low back pain patients and found that patients who report high levels of attention to pain also report higher pain intensity, increased use of health-care resources and more emotional distress. Vigilance to pain was a significant predictor of disability, distress and use of health-care resources.[33] Hypervigilance or excessive attention to threat has also been offered as a possible explanation for the dominant anxiety and poor concentration observed in patients with diffuse idiopathic or fibromyalgia pain.[44] [66] One test of this hypothesis found that fibromyalgia patients reported a lower threshold and higher tolerance to an experimentally induced pain than did a sample of patients with rheumatoid arthritis, who, in turn, reported lower threshold and higher tolerance than a non-pain control sample.[34] Using a different measure of attention to pain, we have found in our laboratory that patients who attend frequently towards diffuse bodily sensation are much more vulnerable to repeated interruption by high-intensity pain.[14] Heightened and habitual attention to pain and bodily sensation is associated with high levels of disability and distress for patients with chronic pain.

Catastrophizing and worry

The consequences of repeated attention to threat may be the development of a fixed pattern of responding to threatening stimuli and pain. One particular response to threatening pain, which is proving to be predictive of the severity of complaint of pain, has been termed 'catastrophic thinking' or 'catastrophizing'. Put simply, this is a habitual, almost immediate, appraisal of a situation as extremely and globally catastrophic. Sullivan and colleagues have developed a measure of catastrophic thinking about pain that assesses the extent to which we magnify the outcome and effects of pain, consider ourselves helpless to respond, and have little control over whether we think this way or not.[51] They conducted two experiments, the first with pain-free students, who they subjected to a cold-pressor procedure, and the second with patients undergoing an aversive medical procedure. They found that catastrophizers reported significantly more negative pain-related thoughts, more distress and higher pain intensity compared with non-catastrophizers. Keefe and colleagues have used a different measure of pain control and catastrophizing in studying clinical populations. For example, they studied patients with rheumatoid arthritis who had undergone knee replacement surgery and found that those who rarely catastrophized had much lower levels of pain and disability than patients who catastrophized often.[23] Recently, we have argued that catastrophic thinking can usefully be understood as an extreme form of a normal process of worrying about pain. Chronic worry about pain and how to solve the problem of pain may lead to a pattern of catastrophic thinking.[2]

Avoidance

One consequence of the urgency effect of pain, the fact that pain demands a change of behaviour, is that patients with pain avoid pain-inducing activity. A number of studies now show that the pain alone is insufficient to explain disability and avoidance. McCracken and colleagues, for example, demonstrated that the fear of pain made a unique and significant contribution to the prediction of disability.[32] Taking this further, some authors have argued that the fear of pain is more disabling than pain itself.[62] In a recent study of this idea, Crombez and colleagues replicated the finding that pain-related fear is a better predictor of disability than pain, but also extended the findings to a behavioural performance test. They showed that, when instructed to engage in a behavioural performance task that involves musculoskeletal loading, chronic low back pain patients performed poorly on the task. Poor behavioural performance was predicted by elevated levels of fear of (re)injury due to movement and the fear of the effect that physical activity would have on the pain.[7] Pain-related fear is thought to mediate the effects of pain upon performance. A recent authoritative review of this emerging field argues that the avoidance of pain or injury-inducing activity is a normal mechanism of survival. However, when pain becomes chronic, those with marked fear of pain chronically avoid activity that leads to disability. Counter-intuitively, in many cases of chronic non-malignant pain, it may be more healthy to confront or engage in physical activity that, in the short term, produces pain and the fear of pain and (re)injury.[60]

Depression

The experience of pain and the threat of pain can lead to negative or low affect. Chronic low affect, including persistent feelings of frustration and anger and negative or destructive self-appraisal are common effects of persistent pain. Unsurprisingly, the majority of adult chronic pain patients who present for treatment at pain clinics are also depressed to some degree. However, this depression is not brought about directly by the pain severity but by the disabling consequences of how one reacts to the chronic pain.[57] There are a number of facets of depression that are important in understanding the pain patient.

Anger

Anger is not always associated with depression. However, it is included here as the angry pain patient is often poorly understood. Anger is a relatively common experience for pain patients and so, in turn, for the pain professional. Where there is no clear immediate object of anger (e.g. an aggressive other person or an immediate agent of injustice), it is often associated with global frustration and hostility, feelings of aggression and a feeling of being blamed. Anger in chronic pain patients is often unrecognized as a means by which patients attempt to claim self-control or self-esteem. Anger and hostility can have significant deleterious effects upon both health and treatment effectiveness.[17] Treatment of the very angry patient requires a high degree of trust and honesty in an environment of cynicism and hostility. Aggression and overt anger often increase the probability of treatment ineffectiveness as either patient or therapist will withdraw from therapeutic contact, thereby fuelling anger. Treatments designed for the chronic pain patient should directly address in some form the effects of anger and frustration.[63]

Self-denigration

A key component of depression is the extent to which individuals appraise their self-worth and abilities negatively (e.g. 'I'm useless and pathetic', 'I'll never be able to control this pain'). Early research suggested that negative self-appraisal may promote a self-fulfilling prophecy in which patients learn to be helpless and hopeless. Research with rheumatological patients did not find any convincing evidence for this case.[49 52] Rather, recent evidence indirectly suggests that what may be important about depression in chronic pain is the extent to which the pain refers critical judgement onto the self. Recent experimental studies demonstrate that patients have specific, not global, memory biases for pain information that refers negatively to the self.[42] Although a focus on the specific self-denigrating effects of depression and pain is only now being developed and data are certainly needed, it could have far-reaching effects on current self-management approaches to chronic pain. Simply instructing patients that the route to successful management of pain lies with them may be an invitation to fail. Indeed, many pain patients, when presented with the idea of self-management, first understand this to mean a threat to their worthiness for treatment.[13]

Coping

The term 'coping' is often used to denote two similar events. First, it is understood to mean anything that one does in response to a stressful event, regardless of its efficacy in removing the stressor or in relieving the stress response. Secondly, it is understood to mean a positive effect of either removing the stressor or relieving the stress response.[37 38] Here I take it to have the first meaning. Whenever we are faced with a stressful event such as pain, or the fear of pain, we respond. This response can have both positive and negative effects. The personality variables discussed above will have a strong effect on the response people make to pain and/or the fear of pain. However, the search for patterns of responding or types of responding has also included other ideas worth mentioning.

Action and control

First, the idea that there are passive and/or active ways of responding is commonly held. Patients who are passive in response to threat show greater distress and disability than patients who attempt to solve problems.[50] Similarly, those who believe that they have the personal ability to have control over pain also show improved function and fitness.[10] One interesting investigation found that if women in active labour are given some control over parts of the delivery process, positive effects can be seen in terms of reduced pain, reduced tiredness and increased energy even if this control is only at the level of monitoring.[27] Taking some control over the cause of pain or the method of analgesia has a beneficial effect. Those who respond actively to pain or the fear of pain are more likely to adjust effectively.

Information and predictability

Related to whether one takes action or takes part in analgesic procedures is the effect of whether one seeks to predict the effects of pain or whether one prefers to be distracted. Many experimental studies of the possible effects of distraction from, or attention to, pain and analgesia have been conducted. The key finding is that both approaches can be effective. However, the most important finding suggests that only those strategies that fit with a person's preferred or habitual method will be effective. For example, if someone is used to managing the pain of dentistry by thinking of anything else but dentistry, giving the patient detailed information about the procedure will simply undermine an effective strategy. Crombez and colleagues reported an interesting study of what information it might be useful to have for those who pay attention to the pain.[6] They found that information about the sensation of the expected pain did not improve the reaction to the pain. However, knowing how long a pain will last did improve the reaction to the pain.

Making sense of the pain

People are intrinsically motivated to make sense of experience. Except in extreme cases of depression or in specific circumstances of prolonged restriction or incarceration, people are motivated to reach an understanding of personal events. Until a pain is understood within a system of knowledge, it will interrupt current thinking and promote worry and concern. Knowing what has caused a pain and what it may mean and does not mean is critical for effective coping. Those patients who are most difficult to help are those who repeatedly present with problems that have no known aetiology.[48] Not knowing compounds distress and an uncertain diagnosis leads to an increased belief in illness.[5]

Clinical implications for acute pain management

The experience and expression of pain are complicated, multifactorial events. However, most clinicians ignore these factors and do not attempt to harness their effects. Worse still, there is a large industry dedicated to the eradication of these effects as they pollute otherwise neat designs for testing the effects of pharmacological agents upon an analgesic response. For it is these effects that make up the placebo element of all analgesics.[43] Unfortunately, the efforts to limit the placebo effect rather than understand and control it may be throwing the baby out with the bath-water.[35]

Perhaps a certain ignorance of the psychological factors is understandable. One could suggest that in most acute pain situations these factors take care of themselves and do not need attending to. I would go further and suggest that, even if the pain relief was not psychologically optimal, then in most cases it is unlikely to lead to any long-term psycho-

Table 1 Using psychological factors in clinical practice

Vigilance to pain	Patients are distracted by the pain and are urged to react. Pain patients will have impaired concentration as they are being interrupted constantly by an aversive stimulus. Keep all communications clear and brief. Repeat key points often. Expect patients to talk about the pain often, as it is being brought repeatedly into attentional focus for them. This is not a sign of a somatization disorder or hypochondria.
Avoidance	Patients will naturally avoid pain and painful procedures. Be aware that this will occur and plan for it. Painful treatments will be avoided and patients will compensate for any disability caused by avoidance (e.g. shifted body weight distribution). If a habitual pattern of avoidance develops, this may lead to chronic pain. Patients must be given an understanding that pain does not necessarily equal damage. A credible medical authority must deliver this message.
Anger	Patients with pain may shout at you, abuse you and generally be hostile to you. If they are hostile to you they have probably been hostile to everyone. Most often this will have nothing to do with you, and you will need to understand that anger normally means extreme frustration, distress and possibly depression. Anger functions to push people away and isolate a person. The angry pain patient is therefore less likely to have received or heard any information about their problems and be more confused than the non-angry patient.
Involve the patient	First, assess the patient's normal way of coping with pain by simply asking how he or she has coped with predictable pain, such as a visit to the dentist. Secondly, match your strategy to the patient's preference. If the patient needs information, inform them how much pain they may expect to feel, what it may feel like and, critically, for how long (if this information is known). Always slightly overestimate the time rather than underestimate it. Finally, if possible, involve the patient in the delivery of any pain management strategy.
Make sense of the pain	Always ask the patient what they know and fear about the cause of the pain, the meaning of the pain and the time course of the pain. Expect the unexpected. What makes sense to one person is nonsense to another. What matters is that it is their understanding, not yours, that will inform their behaviour. Uncertain diagnoses or unknown diagnoses will lead to increased vigilance to pain and increased symptom reporting.
Consistency	Develop a consistent approach to clinical information, patient instruction and patient involvement within pain management. Practice should be consistent for each patient and from each member of the pain team, over time.

logical damage. However, there are certain cases where a working and applied knowledge of the above factors can improve the patient's distress and function, reduce pain and fear of pain, improve the effectiveness of non-psychological analgesics and reduce physician distress. Table 1 offers a clinical summary of how the above knowledge may be used to best effect in everyday practice.

Although there is a plausible argument to be made that in many acute pain situations the psychological factors are of less importance for the busy clinician to attend to, for chronic pain they are unavoidable and of critical importance. Of the population of patients who report persistent and unremitting pain that has lasted for 6 months or longer, a large and growing number are highly distressed and repeatedly present for a wide range of treatments.[9 61]

Chronic pain

In addition to experiencing pain, chronic pain patients who present for treatment are often disabled and report other associated problems, such as sleep difficulties and fatigue.[37] Over time they may have become interpersonally isolated and have developed unsatisfactory family roles and responsibilities.[26] It is common that an untherapeutic reliance upon social and medical support systems develops in which people continue to seek and receive treatment.[47]

The persistent attempts to react and adapt to pain and its widespread destructive consequences often result in a range of emotional problems, such as depression and pain-related fear. Interestingly, chronic pain patients have an elevated presentation of other phobic responses, such as the fear of social interaction, leaving secure environments, blood, illness and death.[3] Chronic persistent pain, fear and depression inevitably have negative effects on other aspects of cognition. Patients commonly complain of poor concentration,[25] poor memory[46] and increased failure to complete cognitive tasks.[11]

For patients with this complex or syndromal presentation, the treatment of choice is cognitive behaviour therapy, preferably delivered at an interdisciplinary pain management centre. Without the input of such an interdisciplinary team, the dangers of ineffective or harmful treatments are significantly increased as patients persist in seeking a cure for an incurable pain.[29] For such patients, the focus of treatment should be shifted away from the pain towards the detrimental effects of pain. Table 2 outlines the domains of a pain experience that are the targets of therapy.

There exist reliable instruments for each of these domains of experience, and it is recommended that in routine non-psychological practice the effect of pain upon these domains is assessed and that the effects of any treatment upon these domains is also assessed. Assessment of the chronic pain patient and the performance of current instrumentation has been reviewed comprehensively.[68] With the exception of pain experience, the remaining six domains are the typical targets of treatment for a programme of cognitive behavioural therapy (CBT). Although CBT is increasingly common for the treatment of young children and adolescents with chronic pain, it is rarely found in a programmatic form.[64] Pilot work in this area does, however, seem promising.[30] For the present, the description of the critical factors of cognitive behaviour therapy and the evidence for

Table 2 Domains of chronic pain experience. Adapted from Morley and colleagues[38]

1. Pain experience	Subjective pain expressed in terms of its intensity, sensory quality and unpleasantness.
2. Mood/affect	Current depression and situational anxiety and longevity of depression and anxiety can be measured. Specific fear responses, such as fear of movement, can also be important to assess.
3. Existing coping methods	Patients respond to pain and threat in a relatively ordered and predictable way. Existing coping strategies and styles, such as the extent of passivity and negative appraisal and the extent of catastrophic thinking and problem-solving ability, can be assessed.
4. Pain behaviour	Overt behavioural acts associated with pain should be assessed as a communication of current distress and as a factor in eliciting others' coping responses. Disability and function should also be assessed using standard self-report instruments and, wherever possible, objective measures.
5. Physical fitness	In some conditions it may be important to measure the effects of pain or treatment on biological measures of disease or fitness.
6. Social role functioning	Pain changes all social role functioning. Key areas that respond to treatment are employment contribution, marital satisfaction, sociability, parental stress and styles of family coping with illness.
7. Health-care behaviour	This specific class of behaviour should be separated from the general class of pain behaviour because it is a critical factor in pain experience and in pain treatment. Key areas are the use of prescribed and over-the-counter medications, visits to general practitioners, and repeat and routine visits to pain clinics.

its effectiveness will be reviewed for adults with chronic pain only.

Cognitive behaviour therapy

'Cognitive behaviour therapy' is a compound term for the selected combination and integration of treatments aimed at reducing or extinguishing the influence of the factors that maintain patients' maladaptive behaviours, beliefs and patterns of thought. Often this treatment is organized as a programme of therapy and is delivered by a team of pain therapists, including anaesthetists, clinical psychologists and physiotherapists. Pain management programmes vary in content and duration as they are often tailored to local populations and specific client groups. They are also commonly constrained by practical and financial contingencies and the currently poor availability of suitably trained and competent staff.

What is important to convey here about this treatment is not so much the specific content of each individual session, but the underlying process that structures the therapy. The seven key factors addressed in a successful programme will now be described.

Direct positive reinforcement of pain behaviour

All overt behaviours communicate pain to others, including tone and content of speech, gait and posture, facial expression and the use of medical aids. Often, the consequences of pain behaviours are detrimental for the patient and add to suffering. A CBT environment would be sensitive to the situations in which patients are directly reinforced for pain behaviours and would seek to minimize their effects.

Indirect positive reinforcement of pain behaviour

Avoidance behaviour is the most common form of reinforcement of pain and disability. Patients will continue to avoid pain-eliciting situations, believing this avoidance to be analgesic when in fact it promotes further pain. Patients develop a symptom-contingent pattern of activity: doing more when one feels good and less when one is in more pain. Over time, this leads to a steady decline in overall activity. These patterns are replaced within CBT by encouraging patients to behave time-contingently and to plan for achievable goals. Successes can then be reinforced.

Positive reinforcement of well behaviour

Chronic pain patients are rarely reinforced for well behaviours. Most staff members are trained to attend to problems and family members are used to responding to need rather than wellness. Lack of reinforcement of health behaviours extinguishes or diminishes the behaviour. In a CBT environment, staff should be trained to recognize and reinforce well or healthy behaviour. They should also be trained to encourage patients and family members to be self-assessing and self-reinforcing of well behaviour.

Physical fitness and function

Chronic pain patients typically lose any sense of normal sensation and normal physical stress and strain. Therefore, the unfit and sedentary patient will experience many symptoms of physical disuse that can be regarded as pain-related and potentially harmful. Increasing general fitness is thought to reduce fatigue and reduce the number of fatigue-related somatic symptoms that can be judged to be pain related. Personal achievement in fitness and function are common goals for patients and can often provide a first point of positive reinforcement and self-reinforcement.

Cognitive reframing

Patients are encouraged to develop insight into the automatic nature of self-defeating and self-denigrating patterns of thinking. Patients are then encouraged to test the reality of these patterns of thinking and develop ways of challenging the premises from which these thoughts arrive. This principle of developing a controlled metaperspective in which one can understand the effects of thoughts upon feelings and feelings upon thoughts underpins a number of the typical contents of therapy, including communication skills, improved problem identification and problem solving, anger management, stress reduction, and the development of a self-relaxation response.

Education and empowerment

Often, a first stage in treatment is to provide a credible rationale for treatment. Education alone is not an effective treatment for chronic pain. However, an understanding of the self-management approach is essential. Key areas that are commonly addressed are the causes and consequences of pain, managing doctor–patient communications, anatomy and biomechanics, the rules of social interaction, and sleep hygiene.

Critical process factors

In addition to these six therapeutic principles that underpin the content of specific sessions in a typical programme of CBT, there are also a number of factors that determine the process or successful delivery of the therapy. Any therapy must be clearly directed and all staff should operate under a consistent set of principles. The more experienced the staff, the better the therapy will be. Similarly, if staff have been trained for this specific treatment rather than having general training, the therapy will be more effective. Regular structured supervision for all team members should be compulsory because the difficulties and distress of patients are often transferred to team members. Conflicting models of treatment should be avoided. For example, changing an analgesic regime in the middle of a CBT programme would undermine the development of self-reinforcing well behaviour. In all cases, CBT should be understood as the beginning of a lifestyle change, and appropriate maintenance of change components should be included.

The evidence base

There are three meta-analyses and reviews of the effects of CBT in chronic pain. The first included all non-medical trials and uncontrolled trials.[31] The second addressed only psychological treatments and also included uncontrolled trials.[18] The third focused upon only randomized controlled trials of psychological and educational treatments in a primary care setting.[58] The two meta-analyses that included non-randomized controlled trials found that the largest treatment effect sizes were for changes in mood, behaviour and pain, with smaller treatment effect sizes for use of health-care resources. The third meta-analysis reported similar findings with the exception of the finding for mood.

We conducted a systematic review and a meta-analysis of all randomized controlled trials of cognitive behaviour therapy for adults with chronic pain.[38] Excluded were trials of therapy for chronic headache as these have different targets of therapy, where lasting pain relief is a realistic target. In all, there were 33 published randomized controlled trials, of which 25 gave analysable data. Most trials used either a waiting list control group or another treatment. All domains of chronic pain experience (Table 2) were coded for effect sizes. Compared with a no-treatment control, CBT produced significant effect sizes in all domains. Compared with another treatment, CBT produced significant effect sizes for the domains of pain, coping and pain behaviour. We concluded that 'published randomized controlled trials provide good evidence for the effectiveness of cognitive behaviour therapy and behaviour therapy for chronic pain in adults'. It is worth noting that these effect sizes are of a similar size to those found in the psychotherapy research literature and are high when compared with non-psychological treatments for chronic pain.

There is no shortage of evidence for the effectiveness of CBT on the range of domains of chronic pain experience. However, the challenge for effective CBT for the management of chronic pain comes with the delivery of effective treatment programmes. CBT is complex, lengthy and highly variable and is critically dependent upon the quality and training of staff and the appropriate content of therapy. Currently, there exists no national standard for treatment effectiveness and no requirement for audit and improvement. However, the effectiveness of appropriately designed and competently delivered CBT is well established and recent policy has strongly recommended its inclusion in routine pain clinic work.[4 8 29]

The next generation of CBT for the treatment of chronic pain will need to include a clear recognition that this treatment is designed for long-term changes, and so will need to include methods of reducing relapse and attrition from treatment. Further treatment will also need to address and quantify the effects of critical process variables, such as patient adherence to treatment and the therapists' use of evidence-supported protocols. Perhaps the most significant challenges in the development of improved CBT are the ability to tailor treatments to individual needs and to develop treatment programmes for specific groups such as children.[45 54–56]

Summary and conclusion

Psychological factors are central to the experience of pain, the delivery of effective analgesia and for the specific treatment of chronic pain and disability. Improvement in pain management can often be brought about by very simple, if subtle, changes in clinical practice. Although simple, these changes can have significant effects in the experience of pain, distress and use of health-care resources. For the chronic pain patient, the presentation is much more complex and the treatment interdisciplinary and programmatic. The evidence for the effectiveness of cognitive behaviour therapy for adults with chronic pain is now well established. This treatment should be available as a core part of any chronic pain service.

References

1 Aldrich S, Eccleston C. Making sense of everyday pain. *Soc Sci Med* 2000; **50**: 1631–41

2 Aldrich S, Eccleston C, Crombez G. Worrying about chronic pain: vigilance to threat and misdirected problem solving. *Behav Res Ther* 2000; **38**: 457–70

3 Asmundson GJG, Norton GR, Jacobson SJ. Social, blood/injury, and agoraphobic fears in patients with physically unexplained chronic pain—are they clinically significant? *Anxiety* 1996; **2**: 28–33

4 Audit Commission. Anaesthetic services in the UK. London: Department of Health, 1998

5 Cioffi D. Asymmetry of doubt in medical self-diagnosis: the ambiguity of 'uncertain wellness'. *J Pers Soc Psychol* 1991; **61**: 969–80

6 Crombez G, Baeyens F, Eelen P. Sensory and temporal information about impending pain: the influence of predictability on pain. *Behav Res Ther* 1994; **32**: 611–22

7 Crombez G, Vlaeyen JWS, Heuts PHTG, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain* 1999; **80**: 329–39

8 Clinical Standards Advisory Group. *Services for Patients with Pain*. London, 2000

9 Davies HTO, Crombie IK, Macrae WA, Rogers KM. Pain clinic patients in Northern Britain. *Pain Clin* 1992; **5**: 129–35

10 Dolce JJ. Self-efficacy and disability beliefs in behavioural treatment of pain. *Behav Res Ther* 1987; **25**: 289–99

11 Dufton BD. Cognitive failure and chronic pain. *Int J Psychiatry Med* 1989; **19**: 291–7

12 Eccleston C. The attentional control of pain—methodological and theoretical concerns. *Pain* 1995; **63**: 3–10

13 Eccleston C, Williams AC de C, Stainton Rogers W. Patients' and professionals' understandings of the causes of chronic pain: blame, responsibility and identity protection. *Soc Sci Med* 1997; **45**: 699–709

14 Eccleston C, Crombez G, Aldrich S, Stannard C. Attention and somatic awareness in chronic pain. *Pain* 1997; **72**: 209–15

15 Eccleston C, Crombez G. Pain demands attention: a cognitive–affective model of the interruptive function of pain. *Psychol Bull* 1999; **125**: 356–66

16 Engel GL. 'Psychogenic' pain and the pain-prone patient. *Am J Med* 1959; June: 899–918

17 Fernandez E, Turk DC. The scope and significance of anger in the experience of chronic pain. *Pain* 1995; **61**: 165–75

18 Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. *Pain* 1992; **49**: 221–30

19 Fordyce WE, Fowler RS, Lehmann JF, DeLateur BJ. Some implications of learning in problems of chronic pain. *J Chronic Dis* 1968; **21**: 179–90

20 Gamsa A. The role of psychological factors in chronic pain. 1. A half-century of study. *Pain* 1994; **57**: 5–15

21 Gamsa A. The role of psychological factors in chronic pain. 2. A critical appraisal. *Pain* 1994; **57**: 17–29

22 Goldman A, Lloyd Thomas AR. Pain management in children. *Br Med Bull* 1991; **47**: 676–689

23 Keefe FJ, Caldwell DS, Martinez S, Nunley J, Beckham J, Williams DA. Analysing pain in rheumatoid arthritis patients. Pain coping strategies in patients who have had knee replacement surgery. *Pain* 1991; **46**: 153–60

24 Keefe FJ, Salley AN, Lefebvre JC. Coping with pain: conceptual concerns and future directions. *Pain* 1992; **51**: 131–4

25 Kewman DG, Vaishampayan N, Zald D, Han B. Cognitive impairment in musculoskeletal pain patients. *Int J Psychiatry Med* 1991; **21**: 253–62

26 Kraaimaat FW, Bakker AH, Janssen E, Bijlsma WJ. Intrusiveness of rheumatoid arthritis on sexuality in male and female patients living with a spouse. *Arthritis Care Res* 1996; **9**: 120–5

27 Leventhal EA, Leventhal H, Shacham S, Easterling DV. Active coping reduces reports of pain from childbirth. *J Consult Clin Psychol* 1989; **57**: 365–71

28 Levine JD, Gordon NC, Smith R, Fields HL. Post-operative pain: effect of extent of injury and attention. *Brain Res* 1982; **234**: 500–4

29 Loeser JD. Mitigating the dangers of pursuing cure. In: Cohen MJM, Campbell JN, eds. *Pain Treatment Centers at a Crossroads: A Practical and Conceptual Reappraisal*. Seattle: IASP Press, 1996; 101–8

30 Malleson PN, Connell H, Bennet S, Eccleston C. Chronic idiopathic pain syndromes. *Arch Dis Child* 2001; **84**: 193–9

31 Malone MD, Strube MJ. Meta-analysis of non-medical treatments for chronic pain. *Pain* 1988; **34**: 231–44

32 McCracken LM, Zayfert C, Gross RT. The Pain Anxiety Symptoms Scale: development and validation of a scale to measure fear of pain. *Pain* 1992; **50**: 67–73

33 McCracken LM. 'Attention' to pain in persons with chronic pain: a behavioural approach. *Behav Ther* 1997; **28**: 271–84

34 McDermid AJ, Rollman GB, McCain GA. Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. *Pain* 1996; **66**: 133–44

35 McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68**: 217–7

36 Melzack R. *The Puzzle of Pain*. London: Penguin, 1973

37 Moldofsky H, Lue F, A. Disordered sleep, pain, fatigue, and gastrointestinal symptoms in fibromyalgia, chronic fatigue and irritable bowel syndromes. In: Mayer EA, Raybould HE, eds. *Basic and Clinical Aspects of Chronic Abdominal Pain*. New York: Elsevier Science Publishers, 1993; 249–55

38 Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomised controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999; **80**: 1–13

39 Morris DB. The culture of pain. Berkeley (CA): University of California Press, 1991

40 Ng B, Dimsdale JE, Rollnik JD, Shapiro H. The effect of ethnicity on prescriptions for patient-controlled analgesia for postoperative pain. *Pain* 1996; **66**: 9–12

41 Parmelee PA, Smith B, Katz IR. *Pain* complaints and cognitive status among elderly institution residents. *J Am Geriatr Soc* 1993; **41**: 517–22

42 Pincus T, Pearce S, McClelland A, Isenberg D. Endorsement and memory bias of self-referential pain stimuli in depressed pain patients. *Br J Clin Psychol* 1995; **34**: 267–77

43 Richardson PH. Placebo effects in pain management. *Pain Rev* 1994; **1**: 15–32

44 Rollman GB, Lautenbacher S. Hypervigilance effects in fibromyalgia: pain experience and pain perception. In: Voeroy H, Merskey H, eds. *Progress in Fibromyalgia and Myofascial Pain*. New York: Elsevier Science Publishers, 1993; 149–59

45 Roth A, Fonagy P. What works for whom? A critical review of psychotherapy research. New York: Guilford Press, 1996

46 Schnurr RF, MacDonald MR. Memory complaints in chronic pain. *Clin J Pain* 1995; **11**: 103–11

47 Sharpe M, Bass C. Pathophysiological mechanisms in somatization. *Int Rev Psychiatry* 1992; **4**: 81–97

48 Sharpe M, Mayou R, Seagroatt V, *et al.* Why do doctors find some patients difficult to help? *Q J Med* 1994; **87**: 187–93

49 Skevington SM. Depression and causal attributions in the early stages of a chronic painful disease: a longitudinal study of early synovitis. *Psychol Health* 1993; **8**: 51–64

50 Snowturek AL, Norris MP, Tan G. Active and passive coping strategies in chronic pain patients. *Pain* 1996; **64**: 455–62

51 Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995; **7**: 524–32

52 Tayer WG, Nicassio PM, Radojevic V, Kralsi T. Pain and helplessness as correlates of depression in systemic lupus erythematosus. *Br J Health Psychol* 1996; **1**: 253–62

53 Tunks E, Bellissimo A. coping with the coping concept: a brief comment. *Pain* 1988; **34**: 171–4

54 Turk DC, Rudy TE. Neglected factors in chronic pain treatment outcome studies—referral patterns, failure to enter treatment, and attrition. *Pain* 1990; **43**: 7–25

55 Turk DC, Rudy TE. Neglected topics in the treatment of chronic pain patients—relapse, noncompliance, and adherence enhancement. *Pain* 1991; **44**: 5–28

56 Turk DC, Rudy TE, Sorkin BA. Neglected topics in chronic pain treatment outcome studies—determination of success. *Pain* 1993; **53**: 3–16

57 Turk DC, Okifuji A, Scharff L. Chronic pain and depression—role of perceived impact and perceived control in different age cohorts. *Pain* 1995; **61**: 93–101

58 Turner JA, Schroth WS, Fordyce WE. Educational and behavioural interventions for back pain in primary care. *Spine* 1996; **21**: 2851–9

59 Unruh AM. Gender variations in clinical pain experience. *Pain* 1996; **65**: 123–67

60 Vlaeyen JWS, Linton S. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain* 2000; **85**: 317–32

61 Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. *Pain* 1988; **32**: 173–83

62 Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A fear-avoidance beliefs questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low-back-pain and disability. *Pain* 1993; **52**: 157–68

63 Wade JB, Price DD, Hamer RM, Schwartz SM, Hart RP. An emotional component analysis of chronic pain. *Pain* 1990; **40**: 303–10

64 Walco GA, Varni JW, Ilowite NT. Cognitive–behavioral pain management in children with juvenile rheumatoid arthritis. *Pediatrics* 1992; **89**: 1075–9

65 Wall PD. On the relation of injury to pain. *Pain* 1979; **6**: 253–64

66 Wall PD. The mechanisms of fibromyalgia: a critical essay. In: Voeroy H, Merskey H, eds. *Progress in Fibromyalgia and Myofascial Pain*. New York: Elsevier Science Publishers, 1993; 53–9

67 Weisberg JN, Keefe FJ. Personality disorders in the chronic pain population—basic concepts, empirical findings, and clinical implications. *Pain Forum* 1997; **6**: 1–9

68 Williams AC de C. Pain measurement in chronic pain management. *Pain Rev* 1995; **2**: 39–63

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Correspondence

Anaesthesia and sleep apnoea

Editor—I read with interest the review article by Loadsman and Hillman[1] regarding sleep apnoea and agree that enquiries into this condition should be made at the preoperative visit to allow planning for potential perioperative problems.

It is stated that a clear understanding of the implications of sleep apnoea is as yet unknown and that some of the treatments may be of limited value and harbour potential complications. This *per se* is a pointer to the need for further research into the subject and a perfectly valid statement.

My concern is that the authors state in summary that 'anaesthetists are ideally placed to screen large numbers of people for sleep disordered breathing ...'. Effective screening requires a condition that is easily defined, whose implications are known, and for which there is clear treatment regimen: none of these apply to sleep apnoea.

I. Taylor
Perth
Western Australia

1 Loadsman JA, Hillman DR. Anaesthesia and sleep apnoea. *Br J Anaesth* 2001; **86:** 254–66

Editor—We read with interest the review of anaesthesia and sleep apnoea by Loadsman and Hillman.[1] They list stroke, cerebral palsy, head injury, Shy-Drager syndrome, poliomyelitis, myotonic dystrophy, dysautonomia and tetraplegia as known and suspected predisposing conditions for obstructive sleep apnoea. Poliomyelitis, amyotrophic lateral sclerosis, and muscular dystrophy are listed as causes of central sleep apnoea.

We suggest that Charcot Marie Tooth neuropathy (CMT) (type 1a) should be included as a predisposing condition for sleep apnoea syndrome. CMT is a genetically heterogeneous group of hereditary motor and sensory polyneuropathies. It is the most common inherited polyneuropathy (1/2500).[2] CMT1a is the most common subtype. It is characterized by degeneration of peripheral nerves and roots, resulting in distal muscle weakness, atrophy and sensory impairment. Until recently, sleep apnoea had only rarely been reported in CMT patients, with no causal relationship shown.

Dematteis and colleagues recently published a study of 14 family members of whom 11 had genetically proven CMT1a (autosomal dominant duplication of the chromosome 17p11.2-12 locus leading to overproduction of myelin protein PMP22).[3] All 11 individuals had sleep apnoea syndrome with a mean apnoea-hypnoea index of 46.6 h^{-1} of sleep. This is regarded as severe.[4] Apnoeas were mainly obstructive in nine individuals and central in two. The compound muscle action potential (CMAP) in the median nerve is used to assess the severity of CMT. The study found that sleep apnoea and neuropathy severity were highly correlated. The CMAP amplitude of the median nerve was inversely correlated with the apnoea-hypopnoea index. The severities of CMT and sleep apnoea were greater in male CMT family members. Age and male gender also correlated with sleep apnoea syndrome in the individuals studied. It is notable that only five of the 11 individuals spontaneously complained of symptoms of CMT. A significant proportion of CMT patients never need to seek treatment, as their neuropathic symptoms are unrecognized or trivial. The authors suggest that pharyngeal neuropathy may be the pathophysiological mechanism that links CMT1a and sleep apnoea syndrome and that assessment of laryngeal and pharyngeal nerve function should be undertaken in CMT patients.[3]

Clearly, further research is necessary to clarify the association between CMT and sleep apnoea. CMT is a common neuropathic disease and those severely afflicted not uncommonly require anaesthesia for corrective joint surgery. We suggest that such individuals be questioned regarding symptoms of sleep apnoea prior to anaesthesia, as the worst affected CMT cases may be at greatest risk of perioperative airway obstruction.

David Pogson
Sharon Johnston
Adelaide
Australia

1 Loadsman JA, Hillman DR. Anaesthesia and sleep apnoea. *Br J Anaesth* 2001; **86:** 254–66
2 Pogson DG, Telfer J, Wimbush S. Prolonged vecuronium neuromuscular blockade associated with Charcot Marie Tooth neuropathy. *Br J Anaesth* 2000; **85: 914–7**
3 Dematteis M, Pepin J-L, Jeanmart M, Deschaux C, Labarre-Vila A., Levy P. Charcot-Marie Tooth disease and sleep apnoea syndrome: a family study. *Lancet* 2001; **357:** 267–72
4 AASM taskforce report: sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1996; **22:** 667–89

Editor—Thank you for the opportunity to reply to these comments. Dr Taylor is concerned about our statement regarding the capacity of anaesthetists to screen for sleep disordered breathing. We fear this concern has arisen from a misunderstanding of our text. We did not, as Dr Taylor suggests, state 'that a clear understanding of the implications of sleep apnoea is as yet unknown'. Quite the contrary, we provided whole sections and tables devoted to the symptoms, signs and sequelae of sleep disordered breathing. What we did say was that 'understanding of the implications of sleep disturbance and sleep disordered breathing *for perioperative morbidity and mortality* is limited' which is, of course, a very different matter. While we did, as Taylor says, point out that *some* of the treatments are of limited value and harbour complications, we also detailed a number of very effective therapies for sleep disordered breathing. While its milder forms may be hard to detect and have minimal consequences, moderate to severe sleep apnoea is well defined, associated with substantial morbidity and readily treated. It is common, with 4% of middle-aged men affected. Anaesthetists, with their interest in the upper airway and capacity to observe its behaviour under anaesthesia and sedation, are in a good position to identify patients who might benefit from further investigation.

Pogson and Johnson highlight a further example in a long list of neuromuscular disorders that may contribute to obstructive sleep apnoea or sleep-related hypoventilation. We mentioned neuromuscular disorders in general as causes of these conditions and gave some examples, but we concede that this list was not exhaustive. We reiterate that *any* patient with a neuromuscular disease affecting respiratory or upper airway muscles is at risk of disordered breathing during sleep.

John A. Loadsman
David R. Hillman
Australia

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Perioperative β-blockade

Editor—The recent editorial in your journal[1] which raises the issue of perioperative β-blockade is a welcome addition to an already crowded debate on this topic. Two editorials from the United States,[2 3] in addition to an editorial in the *British Journal of Surgery* in 2000,[4] have already strongly advocated the use of heart rate control to reduce perioperative cardiac deaths.

Unfortunately, any message seems not to be getting through to clinical anaesthetists in the UK. Ambivalent editorials in the journal of our own Royal College will not help. An in-house audit of practice at our institution revealed that, regardless of the grade of anaesthetist, not one of 50 patients undergoing major surgery who had known ischaemic heart disease or two or more risk factors (as defined by Mangano[5]) received perioperative β-blockade. Fortunately, patients already on these drugs did not have them discontinued prior to induction of anaesthesia. We are left with the question, can we do better?

As we are expected to anaesthetize increasingly older and sicker patients, the number of our patients who are seriously adversely affected by perioperative tachycardia will increase. There seems to be no doubt that perioperative tachycardia is associated with cardiac ischaemia and that this cardiac ischaemia is associated with an increased mortality. The questions seem to be whether we can reliably, safely and cheaply prevent rises in heart rate, and does it matter if we treat patients who are not truly at risk of ischaemia? We feel that the evidence suggests strongly that the answers are 'yes' and 'no' respectively. The possible multiple mechanisms of β-blockers in preventing ischaemia are acknowledged in the editorial, but lack of knowledge about their methods does not obscure their benefits. Can there be a more serious issue, in terms of preventable deaths caused by surgery, for anaesthetists to address?

Howell and colleagues rightly identify that only trials which have true rather than surrogate end-points should influence our practice. Mangano and colleagues' two reports of their double blind randomized trial show a reduction in 2-yr mortality with negligible side effects from atenolol administration,[5 6] surely a solid end-point. Criticism that they stopped patients already on β-blockers is tackled in their discussion: '... excluding all patients receiving preoperative beta blockade does not alter the results.' They continue in the same paragraph, 'atenolol reduced the incidence of myocardial ischemia during postoperative days 0–2 (atenolol 9 placebo 32 $P<0.001$) and days 0–7 (atenolol 16, placebo 37 $P=0.004$)', refuting Howell's assertion that early deaths and adverse events were ignored in the analysis. In-hospital mortality safety endpoints are also addressed in this paper and Mangano's team report that due to low event rates there was no difference between the two groups in deaths (cardiac and non-cardiac), myocardial infarction, unstable angina, congestive heat failure, ventricular tachycardia and stroke. Is it still right to dismiss this as inconclusive? This, together with Raby's paper,[7] strongly implies that in-hospital ischaemia can be reduced in patients by β-blockade even if their risk is shown to be only intermediate.

Concern about the adverse effects of β-blockers should be allayed from Mangano's study where there were 'no detectable increases in side-effects commonly associated with beta-blocker use (third-degree heart block, hypotension, bronchospasm or congestive heat failure) in our patients despite the presence of significant cardiac and pulmonary disease'.

Reluctance to extrapolate from Polderman's[8] study to intermediate-risk patients is understandable but one should remember that their 173 subjects with wall-motion abnormalities on dobutamine testing were recruited from 876 patients (a rate of 20%) who had a *single* risk factor. Even if β-blockade helps saves lives only in the high risk patient perioperatively, surely treating 100 patients to gain such a significant benefit in an unidentifiable group of 20 is worthwhile and should be recommended without resorting to further difficult to perform and interpret trials. Such a course of action is not alien to anaesthetists—how many patients receive preoperative H_2-blockers, antacids and rapid-sequence inductions when only a percentage are at high risk of pulmonary aspiration? If questioned why we take such precautions, anaesthetists quite correctly reply that pulmonary aspiration is such a catastrophe that we should take no chances even in the intermediate-risk patient—it is rightly viewed that it is our responsibility to prevent tracheal soiling. Why is it that perioperative cardiac ischaemia is not viewed similarly as such a catastrophe and that it is our responsibility to do what we can to prevent it? Surely there is enough evidence to stop equivocation in the UK and follow the lead of the USA.

Editorials are, rightly or wrongly, viewed by the 'ground troops' as the directives from the recognized experts in a particular aspect of our profession. Is it not the case that this editorial missed an opportunity to encourage British anaesthetists to at least think carefully and give a practical suggestion about the use of perioperative β-blockade to help prevent perioperative cardiac deaths in susceptible patients?

Lionel Davis
Sergei Jovanovic
Department of Anaesthesia
London
UK

1 Howell SJ, Sear JW, Foex P. Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm. *Br J Anaesth* 2001; **86**: 161–4
2 Warltier DC. β-Adrenergic-blocking drugs, incredibly useful, incredibly underused. *Anesthesiology* 1998; **88**: 2–5
3 Tuman KJ, McCarthy RJ. Individualizing β-adrenergic blocker therapy: patient-specific target-based heart rate control. *Anesth Analg* 1999; **88**: 475–7
4 Jones KG, Powell JT. Slowing the heart saves lives: advantages of perioperative β-blockade. *Br J Surg* 2000; **87**: 689–90
5 Mangano DT, Layug EL, Wallace A, *et al.* Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *New Engl J Med* 1996; **335**: 1713–20
6 Wallace A, Layug B, Tateo I, *et al.* Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology* 1998; **88**: 7–17
7 Raby KE, Brull SJ, Timimi F, *et al.* The effect of heart rate control on myocardial ischaemia among high-risk patients after vascular surgery. *Anesth Analg* 1999; **88**: 477–82
8 Poldermans D, Boersma E, Bax JJ, *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *New Engl J Med* 1999; **341**: 1789–94

Editor—The letter by Davis and Jovanovic questions some of the propositions made in our recent editorial. Any editorial will, of its very nature, represent the authors' views on a given topic; it is the role of the journal editor and reviewers to decide whether the article addresses the issue under discussion and whether it represents a reasonable appraisal of the 'state of the art'. Our editorial was intended to council caution and to advise against the uncritical adoption of perioperative β-adrenergic blockade 'across the board'. While β-blockers may offer benefit to patients with an intermediate risk of perioperative cardiac complications, to assume that this is so without conducting appropriate studies is unscientific and unworthy of modern anaesthesia.

Davis and Jovanovic emphasize the action of β-blockers in controlling heart rate. They link the control of heart rate to the suppression of perioperative ischaemia and suggest that this is mechanism whereby β-adrenergic blockade prevents perioperative cardiac events. While the control of heart rate is undoubtedly important, it is by no means the whole story. Stangeland and colleagues compared infarct size following coronary occlusion in cats who received timolol or alinidine to reduce the heart rate of 40 beats min.$^{-1}$ When compared with control animals, there was a greater reduction in infarct size in the cats that received timolol than in those who received alinidine. The implication is that, while decreased heart rate is important, other mechanisms also contribute to the cardioprotection offered by β-adrenergic blockers. The model that has perioperative myocardial ischaemia as a 'necessary cause' for perioperative myocardial infarction has been challenged.[2] It certainly does not receive unequivocal support from the post-mortem data of Dawood and colleagues.[3]

It cannot be assumed from the evidence of two small studies that β-blockers can safely be given to all patients who might have cardiac disease unless there is a specific contraindication. The number needed to treat for the prevention of perioperative cardiac events in the high-risk patients studied by Poldermans and colleagues was 7.4.[4] The UKPDS study of atenolol and captopril reported non-compliance due to bronchospasm in 1 in 16 patients randomized to β-blockade. Overall, one in three patients in the β-blocker limb of the study had problems with their medication and failed to comply.[5] Although no complications associated with β-adrenergic blockade were reported in the study by Poldermans and colleagues, a zero adverse event rate in 59 patients is consistent with an upper 95% confidence limit for the incidence of adverse events of 5%. The balance of risk and benefits in the high-risk patients studied by Poldermans and colleagues supports the use of β-blockers in this population, but this is a single small study and other studies in this group are probably justified.

The position in patients at intermediate risk of perioperative cardiac complications is far less clear. Because of the low in-hospital event rate, Mangano and colleagues were unable to show short-term benefit from perioperative β-adrenergic blockade. An improvement in a surrogate outcome of perioperative myocardial ischaemia is no substitute for this. They were able to demonstrate an association between perioperative β-adrenergic blockade and improved long-term outcome but the validity and generalizability of this finding have been challenged, not least in a well argued paper by Fleisher.[6] Among the points that Fleisher raises is the fact that the placebo group had a higher incidence of coronary artery disease and a significantly lower incidence of β-blocker therapy preoperatively. Following discharge, the placebo group continued to have a lower incidence of β-blocker therapy on long-term follow-up. The survival benefit reported by Mangano and colleagues could be due to long-term therapy in patients with established coronary artery disease (a well recognized indication for β-adrenergic blockade), rather than to the perioperative treatment regimen.

Even if one accepts the findings of Mangano and colleagues, the concerns about safety do not evaporate. The implication of their study is that β-blockers should be given not only to patients with established coronary artery disease, but also to those with risk factors for coronary artery disease. While the former is an established indication, the latter is not. In a recent study, Lee and colleagues identified insulin-dependent diabetes mellitus and high-risk surgery as significant risk-factors for perioperative cardiac complications.[7] From their data, the overall incidence of cardiac complications in a patient with insulin-dependent diabetes mellitus undergoing high-risk surgery was 1.1%. If we assume that perioperative β-adrenergic blockade would reduce this complication rate to 0.55%, 180 patients would have to be treated with β-blockers to prevent one complication. This may be justified. Beta-blockers are cheap drugs, and perioperative cardiac complications may be catastrophic for the patient and expensive for the health service. However, we currently have two randomized-controlled trials, one strong, the other less so, that support this strategy. But we have data from the UKPDS study that suggests that β-blockade may be associated with a relatively high incidence of adverse effects. Further randomized controlled trials are needed before β-blockade becomes the ***sine qua non*** of anaesthesia for patients who may have cardiac disease.

The colleagues of Davis and Jovanovic may be distressed by the implicit criticism of their failure to make more extensive use of perioperative β-blockade. While we hope that perioperative β-blockade does indeed prove to be a major boon to patients who are at risk of cardiac disease and are facing major surgery, we feel more evidence is needed. We understand the caution of those who have not made these drugs part of their everyday practice and would invite them to participate in further trials of this therapy as the opportunity arises.

Simon Howell[1]
John Sear[2]
[1]*University Department of Anaesthesia*
University of Bristol
[2]*Nuffield Department of Anaesthetics*
University of Oxford
UK

1 Stangeland L, Grong K, Vik-Mo H, *et al.* Is reduced cardiac performance the only mechanism for myocardial infarct size reduction during beta adrenergic blockade? *Cardiovasc Res* 1986; **20**: 322–30
2 Fleisher LA ... but, is suppression of postoperative ST segment depression an important outcome? *Anesth Analg* 1997; **84**: 709–11
3 Dawood MM, Gupta DK, Southern J, *et al.* Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996; **57**: 37–44
4 Poldermans D, Boersma E, Bax JJ, *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; **341**: 1789–94
5 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *Br Med J* 1998; **317**: 713–20
6 Fleisher LA. Con: beta-blockers should not be used in all patients undergoing vascular surgery. *J Cardiothorac Vasc Anesth* 1999; **13**: 496–7
7 Lee TH, Marcantonio ER, Mangione CM, *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9

Right heart catheterization in intensive care

Editor—The leading article in the *British Journal of Anaesthesia*[1] very interestingly discussed the difficulties surrounding the proposed PAC-Man randomized-controlled trial (RCT) of the benefits of pulmonary artery catherization (PAC). Not addressed, however, was the fact that PAC is not, in spite of being referred to as such, a therapy: indeed the only allusion to this point was where the author referred to the PAC as a 'monitoring/treatment package'.

PAC is not a treatment. It cannot *per se* confer a benefit on the patient. To suppose that it might is analogous to the belief that some patients have, that a chest X-ray makes them better. The purpose of PAC is measurement of pulmonary capillary wedge pressure (PCWP), cardiac output, or both. Although its use may form part of a 'treatment package', for example in goal directed therapy for sepsis syndrome, it can no more confer a direct benefit than can an arterial line or a saturation monitor. Consequently, any investigation of PAC aimed at assessing outcome benefits associated with it will be misconceived.

It may be that PAC is not used properly, and this has led to an excess of complications which has outweighed the benefits that come from greater knowledge about patients. The way to address this is not to conduct RCTs into use of PAC but to establish the proper indications for use of PAC, then to investigate whether these are being followed. There seem to me to be three main indications, (though there may be more):

- to measure PCWP where there is doubt about the cause of any pulmonary oedema;
- to measure cardiac output, principally in management of goal directed therapy in sepsis syndrome;
- to facilitate precision management of anaesthesia in patients with significant cardiac co-morbidity.

In the first category, indications must be easy to clarify. As to sepsis syndrome, the evidence is now fairly clear about its efficacy. In the last category, it may be that litigation pressures or fees for item of service have led to overuse of PAC: the way to investigate this is not a RCT, but setting clear guidelines and auditing compliance. RCTs grouping all those together, in any event to investigate the therapeutic effect of a non-therapy, cannot possibly provide any clear result.

The second point is closely linked to the first. It is suggested that as PAC is associated with poorer outcomes, it in some way causes poorer outcomes. You might as well say that wet pavements cause rain! Or suggest that as more ICU patients die than do those on the general wards, we should stop doing intensive care. How clear does it have to be? PAC is used in sick patients. Sick patients die. PAC does not stop them all dying (it is not a treatment). So PAC is used in patients with higher death rates. Thus, PAC is associated with higher death rates. This is not a causal association except in so far as PAC use is 'caused by' sick patients.

Christopher Heneghan
Abergavenny
UK

1 Young JD. Right heart catheterization in intensive care. *Br J Anaesth* 2001; **86**: 327–9

Editor—Thank you for the opportunity to reply to Dr Heneghan's letter about my editorial on pulmonary artery catherization. Dr Heneghan is concerned about three aspects of any systematic study of pulmonary artery catheter use. His views are that a pulmonary artery catheter is a monitoring device not a treatment; that deaths attributable to pulmonary artery catheter use are due to misuse or misinterpretation of the data it provides; or that excess mortality in patients who receive a pulmonary artery catheter can simply be explained by case-mix. I will deal with each of these points in turn.

Clearly, a pulmonary artery catheter is only a monitoring device, with an associated risk but no benefit unless the information it provides improves outcome. However, the term right heart catheterization as used in the editorial, and all the cited studies, refers to the package of right heart catheterization and subsequent actions based on the measured variables. It is this package that will be tested by the PAC-Man study. As I explained in the editorial, two study types are possible. In the PAC-Man study the interpretation of data from the right heart catheter and subsequent actions are dictated by the physician and local practice, and the trial is therefore a pragmatic or effectiveness study. The alternative, where all management after insertion of the right heart catheter is determined by a protocol (an efficacy study), is the approach taken in the United States. There are 'pros' and 'cons' to both approaches, but importantly both test the totality of care consequent on right heart catheterization, not just the placement or otherwise of a catheter.

Dr Heneghan also expressed an opinion that any overall detrimental effect of pulmonary artery catheterization may be due to improper use by an unspecified number of other practitioners. This view has been expressed before many times verbally but is not usually committed to print. If a group of 'skilled' users of pulmonary artery catherization are benefiting their patients, but the effect overall is negated or even reversed by a group of 'unskilled' users, then two scenarios follow. The 'unskilled' users must be either a large group whose actions have no effect at all on the patient, or even worse a smaller group who are actually harming their patients by using right heart catheterization. An audit could be used to investigate current practice, but without any prior knowledge of which protocols improve outcome, setting a meaningful standard to audit against is impossible.

I am slightly concerned about the number of times the view that there are 'rogue' users of right heart catherization is expressed. All aspects of medicine require data interpretation, and there will inevitably be a spectrum of abilities amongst practitioners. Making decisions about haemodynamic therapy based on pressure and flow measurements is fundamentally not different from the decision about whether to prescribe any drug based on history, examination and laboratory test results, yet equivocal results from drug trials are never blamed on unskilled prescribers. This spread of abilities among practitioners is, of course, one of many reasons why effectiveness trials often show less benefit than efficacy trials.

Dr Heneghan, in the final paragraph of his letter, suggests that the excess mortality that might be associated with right heart catheterization is simply due to case-mix, in other words only sick people receive catheters and sick people tend to die. Whilst this was true of early case series, mostly involving patients with myocardial infarctions, the science of case-matching has moved on since these studies. The important feature of the Connors' study[1] was that there was an excess of deaths in a group of patients who received right heart catheters compared with an *equally sick* group of patients who did not receive a catheter. The paper would not have received any attention if it were a simple case series. The Scottish study cited[2] showed the same result. As I explained in the editorial, there is a fundamental limitation to case-matching that can only be overcome by randomization, and this is the reason why the PAC-Man study is needed.

Duncan Young
Oxford
UK

1 Connors AF Jr, Speroff T, Dawson NV, *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 1996; **276**: 889–97

2 Mackirdy FN, Livingston BM, Howie JC. The relationship between the presence of pulmonary artery catheters and the case mix adjusted outcome of patients admitted to Scottish ICUs. (Abstract). *Clin Intens Care* 1997; **8**: 9

Internal jugular venous cannulation

Editor—I read with interest the report by Mastan and colleagues[1] describing a misplaced Seldinger wire during attempted placement of an internal jugular venous catheter. The authors state that the Seldinger wire was advanced with minimal resistance. This seems difficult to reconcile with the subsequent discovery, on x-ray and at exploration, that the wire had coiled in the sternocleidomastoid muscle and for some distance subcutaneously. The authors' hypothesis that the J-tip guidewire pierced the wall of the vein also seems implausible. A far likelier explanation is that after successful venous aspiration, while the operator was inserting the tip of the guidewire into the hub of the needle (a tricky procedure at times), the tip of the needle moved and was now located outside the vein.

It is vitally important, during insertion of any central venous cannula, to ensure that the aspirating needle, guidewire and any dilators used are within the lumen of the central vein. Any resistance felt during insertion of the guidewire should prompt suspicion, removal of the wire and repeat aspiration to confirm intravenous tip location. This is especially important during insertion of large bore catheters like pulmonary artery catheter introducers and rapid infusor lines, where unrecognized misplacement can have serious repercussions.

At the University of Michigan, anaesthesia residents are taught to locate the central vein with a 20G cannula-over-needle. After advancing the cannula and removing the needle, the hub of the cannula is connected to a 50 cm length of extension tubing, and the tubing is lowered to allow free flow of blood. The tubing is then held vertically and used as a manometer to ensure that the blood is venous. The tubing is then removed and the guidewire passed through the plastic cannula. This may seem excessively cautious, but it is a very good way to avoid complications and to impress upon inexperienced trainees the importance of meticulous care.

L. Visser
Department of Anesthesiology
University of Michigan Medical Center
Ann Arbor
Michigan
USA

1 Mastan M, Clother PR, Ousta B, Deulkar U. Internal jugular venous cannulation complicated by J-tip wire entrapment. *Br J Anaesth* 2001; **86**: 292–3

Editor—We concur with Dr Visser's comments on J-tip guidewire entrapment during internal jugular venous cannulation. The hypothesis that the J-tip guidewire pierces the wall of the vein does rely on the operating physician's report that the guidewire was advanced with minimal resistance. We also agree that perforation of the vein by the needle tip at the time of guidewire insertion is perhaps the greater risk of this technique.

However, most central venous line sets in our hospital include a cannula over needle design which can be used where risk of needle perforation of the vein is considered to be high. The distance between the needle tip and cannula end in these devices is 3.5 mm (personal communication, Vygon, Gloucestershire) which can be significant when cannulating a collapsed vein. In these circumstances, difficulty may be encountered in advancing the cannula over the needle, if only the needle tip is within the lumen.

The use of a 20 G cannula as recommended by Visser, could increase the chances of cannulating a smaller vein rather than the internal jugular vein. In addition, the diameter of the guidewire available in our central venous line sets is too large to pass through a 20 G cannula.

We are grateful to Dr Visser for his observations and we do agree that the cannula over needle technique does reduce the risk of such complications when used correctly.

M. Mastan
P. R. Clothier
B. Ousta
U. Deulkar
Tameside General Hospital
Ashton-Under-Lyne
Lancashire
UK

Use of the laryngeal tube for nasotracheal intubation

Editor—The Laryngeal Tube (VBM, Medizintechnik, Germany) (Figure 1)[1 2] consists of an airway tube with a small balloon cuff at the tip (distal cuff) and a larger balloon cuff in the middle (proximal cuff). When the device is inserted, the distal tip is positioned in the hypopharynx, the proximal cuff provides a seal by forming a plug in the upper pharynx, and the distal cuff seals the oesophageal inlet. There is a distal aperture in the tube between the two cuffs. We successfully used this device as an aid to fibrescope-aided nasotracheal intubation in a patient in whom tracheal intubation was predicted to be difficult.

A 24-year-old man with multiple fractures of the jaw was scheduled for reconstruction of the jaw and intermaxillary fixation. Difficult tracheal intubation was predicted, since the maximum gap between the incisor teeth was 1.5 cm. Although difficulty in ventilation through a facemask was not predicted, the plastic surgeons asked us to avoid, if possible, thrusting the jaw forward during mask ventilation to minimize worsening of the damage to the jaw. The possibility of awake tracheal intubation was explained to the patient, who consented for insertion of an object into his mouth—but, if possible, not in his nose—before induction of general anaesthesia. Since nasotracheal intubation was necessary, we planned to insert a laryngeal tube while the patient was conscious but sedated, and to intubate the trachea nasally after induction of anaesthesia. The patient was not at increased risk of pulmonary aspiration.

Fentanyl 50 µg and midazolam 2 mg were injected intravenously. The patient became sedated but was responsive to verbal command (a state of conscious sedation). Eight percent lidocaine was sprayed onto the oropharynx. After injection of propofol 50 mg, a size 4 laryngeal tube was passed through the narrowed gap between the teeth and advanced into position with slight resistance. The cuffs were inflated and adequate ventilation confirmed. Insertion of the device did not cause retching and there was no apparent discomfort to the patient. Fibrescopy showed that the device was positioned correctly.

Anaesthesia was then induced by inhalation of an increasing concentration of sevoflurane up to 5% in oxygen via the laryngeal tube. About 10 min later, a 6.0 mm ID reinforced tracheal tube was passed through the nose with great difficulty (due to the narrowed nasal cavity) into the oropharynx. By passing a fibrescope through the tracheal tube, it was easy to identify the distal segment of the laryngeal tube entering the hypopharynx. The fibrescope was

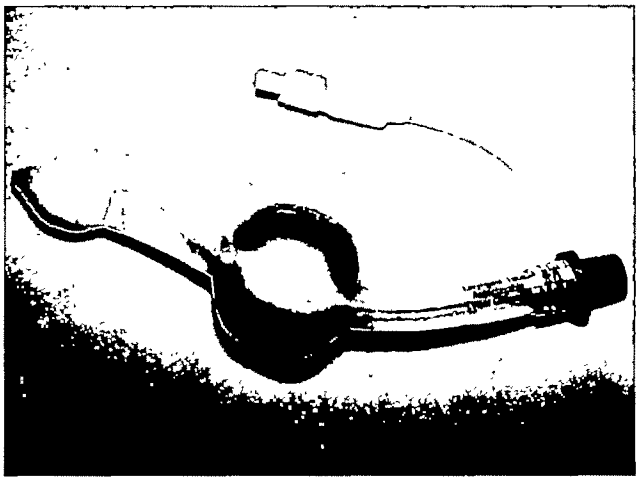

Fig 1 The laryngeal tube.

advanced further into the trachea and the tracheal tube was easily passed over the fibrescope into the trachea. Throughout the procedure, the patient was breathing spontaneously through the laryngeal tube without airway obstruction or desaturation. Time for tracheal intubation (from the start of passing a fibrescope through the tracheal tube to insertion of the tube into the trachea) was 12 s. Correct tracheal intubation was confirmed and the laryngeal tube was removed. The operation proceeded uneventfully. Postoperatively, the patient did not recall any event during induction of anaesthesia.

The laryngeal mask airway[†] can act as a conduit to orotracheal intubation,[3,4] but it does not allow nasotracheal intubation.[5] The cuffed oropharyngeal airway does not obstruct the passage of the fibrescope through the nose to the trachea,[5–7] but manoeuvring of the position of the head, neck and jaw may be required to obtain a patent airway.[8,9] Similarly, a specially tailored facemask which allows insertion of a fibrescope through it[10,11] may require jaw thrusting. In contrast, when the laryngeal tube is used, there is generally no need to support the jaw to obtain a patent airway,[1,2] as in our patient. Insertion of the laryngeal tube was not unduly stressful to our sedated patient. We also found that it was easy to locate the glottis through the fibrescope, since seeing the laryngeal tube indicated that the tip of the fibrescope had entered the oropharynx, and since the glottis should be just in front of the distal cuff of the laryngeal tube. A similar technique using the Combitube has been reported,[12] but insertion of the device under conscious sedation might be stressful.

We believe that in the patient in whom tracheal intubation is predicted to be difficult but awake intubation needs to be avoided, awake insertion of the laryngeal tube and subsequent nasotracheal intubation after induction of anaesthesia (while maintaining spontaneous breathing), is a useful method.

T. Asai
K. Shingu
Department of Anaesthesiology
Kansai Medical University
Moriguchi City
Osaka
Japan

Conflict of interest: The laryngeal tube was a gift from the manufacturer (VBM, Medizintechnik, Germany); no financial support was received.

1 Asai T, Murao K, Shingu K. Efficacy of the laryngeal tube during intermittent positive pressure ventilation. *Anaesthesia* 2000; **55**: 1099–102
2 Dörges V, Ocker H, Wenzel V, Schmucker P. The Laryngeal Tube: a new simple airway device. *Anesth Analg* 2000; **90**: 1220–2
3 Asai T, Morris S. The laryngeal mask airway: Its features, effects and role. *Can J Anaesth* 1994; **41**: 930–60
4 Brain AIJ, Verghese C, Addy EV, Kapila A, Brimacombe J. The intubating laryngeal mask. II: preliminary clinical report of a new means of intubating the trachea. *Br J Anaesth* 1997; **79**: 7042–9
5 Asai T, Matsumoto H, Shingu K. Awake insertion of the cuffed oropharyngeal airway for nasotracheal intubation. *Anaesthesia* 1999; **54**: 492–3
6 Uezono S, Goto T, Nakata Y, Ichinose F, Niimi Y, Morita S. The cuffed oropharyngeal airway. A novel adjunct to the management of difficult airways. *Anesthesiology* 1999; **88**: 1677–9
7 Greenberg RS, Kay NH. Cuffed oropharyngeal airway (COPA) as an adjunct to fibreoptic tracheal intubation. *Br J Anaesth* 1999; **82**: 395–8
8 Asai T, Koga K, Jones RM, Stacey M, Latto IP, Vaughan RS. The cuffed oropharyngeal airway. Its clinical use in 100 patients. *Anaesthesia* 1998; **53**: 817–22
9 Brimacombe J, Berry A. The cuffed oropharyngeal airway for spontaneous ventilation anaesthesia. Clinical appraisal of 100 patients. *Anaesthesia* 1998; **53**: 1074–9
10 Patil V, Stehling LC, Zauder HL, Koch JP. Mechanical aids for fiberoptic endoscopy. *Anesthesiology* 1982; **57**: 69–70
11 Uda R, Ohtsuka M, Minami T, Mori H. Use of a lighted stylet for tracheal intubation through an intubating port of a mask. *Anesthesiology* 1999; **91**: 1560–1
12 Gaitini LA, Vaida SJ, Somri M, Fradis M, Ben-David B. Fiberoptic-guided airway exchange of the esophageal-tracheal Combitube® in spontaneously breathing versus mechanically ventilated patients. *Anesth Analg* 1999; **88**: 193–6

[†] LMA® is the property of Intravent Limited.

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Book Reviews

A Practice of Anesthesia for Infants and Children (third edition). C. J. Cotè, D. I. Todres, J. F. Ryan and N. G. Goudsouzian (editors). Published by W. B. Saunders, Philadelphia. Pp. 777; indexed; illustrated. Price £60.00. ISBN 0-7216-7286-8

This is the latest edition of what is now recognized as a standard textbook. Previous editions in 1986 and 1993 laid the foundations for the present publication which should be an automatic choice for every anaesthetic department in the land, adult or paediatric.

The format of a didactic textbook combined with extensive literature reviews continues and there are thousands of references grouped together at the end of each chapter. Additional chapters have been added and this edition is almost 250 pages longer than its predecessor, even taking account of the fact that the font has been somewhat reduced in size. There are 32 chapters covering all aspects of the subject presented in a logical manner: for example, the chapter on cardiac physiology and pharmacology immediately precedes those on cardiac surgery and anaesthesia, a sensible approach sadly not always seen in other textbooks of a similar genre. The book itself is a sturdy hardback just short of A4 size and has a certain elegance that catches the eye.

One important change has taken place since 1993 in that the editors and contributors do not now work exclusively in Boston and this had markedly improved the standard of some of the chapters. Nevertheless, none of the 49 contributors work outside North America and this has of necessity affected the choice of topics to be covered, for instance malignant hyperthermia takes up the most part of an excellent chapter on temperature control, and the inside end paper contains a reproduction of The Malignant Hyperthemia Association of the United States' guidelines for the emergency treatment of that condition. We, in our small but excellent centre, saw our first case of malignant hyperthermia only a few months ago. Our new, dedicated specialist registrar imagined he was sitting his (old) first part FRCA examination and dealt with the problem admirably.

Most of the chapters have been written by acknowledged experts in their field, indeed the list of contributors reads like a *Who's Who* of North American paediatric anaesthesia. Think 'pain' and Chuck Berde comes to mind; 'muscle relaxants' and Nish Goudsouzian is the first name you think of; 'cardiac surgery' and Paul Hickey; 'day surgery' and Raafat Hannallah, and the list goes on. Some well-known authors of standard textbooks are included amongst the contributors although not all write on what could be thought of as their first choice of topic. Myron Yaster, for example, has redirected his attention from local anaesthesia and narcotics, and writes in this textbook as a co-author on sedation techniques; it is a perfect model of evidence-based didactic teaching offering loads of practical advice. Where no anaesthetist has had the necessary expertise, others with the requisite qualifications have been drafted in to either write, or contribute to, a chapter. This applies especially to perioperative behaviour, burns and an excellent chapter on the pharmacology and pharmacokinetics of drugs in children. The latter includes input from a neonatal pharmacologist and an academic pharmacist.

One long-anticipated improvement is the inclusion of a chapter on the management of the patient with repaired or palliated heart disease written by Maureen Stafford, an anaesthetist who is also a paediatric cardiologist. This is a joy to read. It is full of information about the presentation of the common congenital heart diseases, with explanations of the surgical techniques, complications and residual lesions that may still have to be taken into account when anaesthetising children for non-cardiac procedures. It is fully illustrated and even your reviewer, who now works three sessions per week in the 'cath lab', discovered loads of information, all highly relevant. As with most of the other chapters, there is an extensive literature review with 377 references.

So far so good, but does this rose have any thorns? It may have but the reviewer has failed to find them, despite perusing the reference list to check for undue bias towards North American publications. None was forthcoming, many papers from the UK and Europe are cited. At the time of writing the price is unknown and it may be quite high, with the dollar's strength against the pound, but this is such a complete book that it has to be good value for money no matter how much it costs. No anaesthetic department should be without a copy.

Roddie McNicol
Royal Hospital for Sick Children
Glasgow
UK

Clinical Anesthesia (fourth edition). P. G. Barash, B. F. Cullen and R. U. Stoelting (editors). Published by Lippincott Williams & Wilkins, Philadelphia. Pp. 1576; indexed, illustrated. Price $159. ISBN-07817-22683.

This American multi-author, single volume, textbook of anaesthesia is now in its fourth edition. It comprises 57 chapters and more than 1500 pages. The main theme of the book revolves around general anaesthetic principles of pharmacology and clinical anaesthesia. Issues concerning the safe provision of an anaesthetic service are highly topical and have been included. This book is aimed at the general anaesthetist and it should probably be used as a reference, rather than being read from cover to cover.

There are several chapters which are particularly comprehensive and impressive. Airway management, organ transplantation and pharmacokinetic principles with particular reference to continuous infusions, are well covered. Transoesophageal echocardiography is standard practice during anaesthesia for cardiac surgery in the USA. The trend has been reflected in this book and it was pleasing to read how this technology is being used carefully to refine perioperative anaesthetic and surgical clinical decision-making. The chapters on other aspects of cardiothoracic anaesthesia are covered well, particularly explanations of lung function tests and cardiovascular physiology.

However, there is room for improvement. The book is formidable to read and some areas, especially those on general aspects of anaesthetic care, could be made more concise. Other topics such as 'Critical Care Medicine' and 'Chronic Pain' were too brief and perhaps should have been either extended or excluded altogether. More subheadings would have greatly enhanced the comprehension of the concepts described in the text. In addition, owing to its multi-author nature, there is little cross-referencing between chapters. For example, with the exception of the index, there is no mention of the detailed pharmacogenetics of plasma cholinesterase deficiency in the chapter on muscle relaxants.

For candidates considering this book for the FRCA examination, it should be noted that important areas were not covered. In the chapter on obstetric anaesthesia, the triennial UK Confidential Enquiry into Maternal Mortality and Morbidity was not discussed. This national audit has been on-going for 50 years and has provided valuable information that has influenced anaesthetic

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practice. The chapter on ophthalmic anaesthesia should have had less text and more diagrams, especially for the trainee who is learning how to perform peribulbar and sub-tenon blocks for the first time. Explanations provided in the chapter on monitoring were insufficient to enable the reader to fully understand the principles of invasive blood pressure monitoring. There seemed to be some omissions on important areas in the chapter on trauma and burns. For example, it would have been helpful to see descriptions of the blood supply to the spinal cord, patterns of spinal cord injury and estimation of blood volume requirements during anaesthesia for burns.

Although cardiac risk was discussed in detail, it was a little disappointing that some evaluation of operative risk was not included. Data are currently available on this issue, for example in the P-POSSUM scoring system for non-cardiac surgical patients.

In summary, although this book reflects anaesthetic practice predominantly in the USA, it would nevertheless be appropriate as a reference text for examination candidates in the UK. The authors are to be congratulated on their hard work in producing this latest edition.

Alexander Ng
Graham Smith
University Department of Anaesthesia
Critical Care and Pain Management
Leicester
UK

Handbook of Clinical Anesthesia (fourth edition). Paul G. Barash, Bruce E. Cullen, Robert K. Stoetling (editors). Published by Lippincott Williams & Wilkins, Philadelphia, USA. Pp. 915; indexed; illustrated. Price £39.95. ISBN 0-7817-2918-1.

This book is part of the *Clinical Anesthesia* series, and according to the editors, parallels the parent textbook, *Clinical Anesthesia.* The book is divided into two major sections. The first section is described by the editors as taking the reader in a systematic fashion through the perioperative period, and it achieves this admirably. The second section contains formulae, drug lists, resuscitation protocols, standards of monitoring, a difficult airway algorithm, and a malignant hyperthermia protocol, and these pages have been identified by black ink along the edge of the page to allow rapid reference. Inevitably, with the continuing change in resuscitation protocols, some of these pages will soon be out-of-date. Many authors have contributed to this book, and the editors can be congratulated on the clarity and similarity of layout between chapters. There appears to be very little overlap between them. The use of tables and graphics transmits important information rapidly to the reader, but also preserves the identity of this book as a scientific text and not a pocket-book of key facts, which this book certainly is not. The authors are obviously both experts and regularly practising clinicians in their field, since the information is up-do-date, and their opinions are very sensible and evidence-based on controversial issues. Although this is clearly an American textbook, there is very little that does not translate easily into British practice, and it is reassuring that the huge transatlantic divide that we are told exists for anaesthetic techniques, does not appear that wide in this textbook.

The introduction chapters are concerned with the history of anaesthesia, practice management and resource utilization which includes liability, risk and quality improvement, research issues, and the hazards of the anaesthetists' working environment. Although the management issues relate mainly to American practice, it is interesting to find that the concepts are increasingly being introduced to this side of the Atlantic, and there is plenty of relevant information in these chapters for the British anaesthetist. The section on emotional considerations, which highlights substance abuse and addiction in anaesthetists, is a very sensible inclusion. Chapters II and III are packed full of useful and readable information on the basic scientific principles and pharmacology of anaesthetic practice. The cellular and molecular mechanisms of anaesthesia were extremely clearly presented and summarized. Although there must have been great limitations on space in this textbook, the use of 'real' graphs with measures of scatter displayed to describe experimental data in many of the science chapters, ensures the clarity and believability of text. The bulk of this book (Chapters IV–VI) discusses the clinical practice of anaesthesia and its subspecialties, which includes preoperative evaluation, monitoring, regional and central blockade, postoperative care, and anaesthesia for specialist surgery and specific organ failures, ranging from office anaesthesia to organ transplantation. Again the information presented is detailed and very readable. All textbooks can be criticized for omissions depending on the enthusiasms of the reader, and I would have liked to have seen a description of local anaesthesia for the eye. The problems of anaesthesia for oesophagogastrectomy also required gleaning information from several chapters. The chapter on critical care was very brief although information on the critically ill patient was again available by searching other chapters.

The editors can be congratulated on a very thorough and up-to-date textbook of anaesthesia, and, despite my misguided preconceptions of an American textbook, I found this a valuable source of information, which is hugely relevant to the British anaesthetist. It carries information in a pocketsize format for both teacher and trainee, and has commendable qualities in that information can be rapidly accessed in the clinical environment. It also contains detailed authoritative text, which can be relied upon in both the classroom and examination room. I can recommend this handbook to all anaesthetists.

R. Venn
Worthing
UK

Key Topics in Anaesthesia—Clinical Aspects (third edition). T. M. Craft, P. M. Upton (editors). Published by BIOS Scientific Publishers Ltd, Oxford. Pp. 285; indexed. Price £24.99. ISBN 1-85996-132-0.

This book is a totally reworked third edition in the *Key Topics* series. The two editors have used a total of 14 contributors to produce alphabetically arranged essays on varying clinical topics related to anaesthesia. One hundred and one topics have been chosen and by referring to the Preface of the first edition one can get an understanding of how the topics were selected.

The majority of topics have the same problem-orientated style and the text is neatly broke up with sub-headings. This approach may have a certain appeal for those taking the Final FRCA, searching for help with short-answer questions. There is, however, a lack of the summary tables so often preferred by examination candidates.

This is not a complete textbook and can only be considered an adjunct to examination preparation. There is only one line drawing in the entire book, which makes the book visually unattractive. Even the essay on breathing systems, so easily explained by the appropriate diagram, was devoid of any graphics.

The preface states that the target of the book is for those 'working towards the Fellowship of The Royal College of Anaesthetists'. I feel that the target is narrowed to the final fellowship as this book has little reference to the basic sciences necessary for the Part 1. The discerning final part candidate will also note its far from comprehensive content and may therefore be attracted to the more encyclopaedic tomes on the bookshelves.

As a reference source, the ever-increasing CPD type magazines may provide a more up to date reference guide. The preface suggests that its 'many references for further reading are web sites' to enable the reader to keep up-to-date with current advice. There are 12 web addresses in total.

The Key Topics series has been popular with examination candidates in the past and this edition will help focus the trainee on to a particular subject. The suggested further reading also provides a good source for revision. The preface to the first edition stated clearly the book's objective and recognized its limitations due to lack of completeness. However, candidates may prefer this targeted approach to avoid the overwhelming nature of some textbooks. I am sure this edition will find its niche in many a trainee's armamentarium.

L. M. Gemmell
Wrexham
UK

Key Topics in Accident and Emergency Medicine (second edition). R. Evans and D. Burke. Published by BIOS Scientific Publishers Ltd, Oxford. pp. 344; indexed. Price £24.99. ISBN 1-85996-124-X.

This book which forms part of the *Key Topics* series is written by two accident and emergency consultants, one with a special interest in paediatric accident and emergency medicine. In their preface they explain their intention: to provide the reader with short articles covering a wide variety of topics of particular relevance to the higher specialist trainee but also for nurses and paramedics.

Altogether, there are 94 topics aranged in alphabetical order in this book. Their scope ranges from the general area of 'Obstetric Emergencies,' which is covered in five pages, to the more specific 'Adder Bites' covered in much more detail in four. The topics have a particularly strong accident and emergency character in their scope and nature, for example intraosseous infusion, the management of chemical incidents, drowning and near-drowning, single-dose activated charcoal, and CS gas injury. Tracking down up-to-date information on such a wide variety of subjects will be difficult outside the accident and emergency literature but they are gathered together well in this text. This makes the book particularly useful to the new entrant to the speciality and to those practising elsewhere who want a quick reference to safe practice.

There are, however, important areas of accident and emergency practice not covered in depth or even at all in this book, for example pulmonary embolism, biliary colic and cholecystitis. Bronchiolitis and adult cardiopulmonary resuscitation are other omissions. But a book such as this cannot be comprehensive in breadth or detail. The authors achieve their stated aim through an eclectic, though important series of topics.

A useful collection of established guidelines are scattered throughout, such as those for the management of spontaneous pneumothorax (British Thoracic Society); the management of radiation casualties and chemical incidents (British Association of Accident and Emergency Medicine); and the Ottawa ankle x-ray rules. The content represents current best practice. The references for further reading are useful and up-to-date.

The writing style is clear, didactic and readable. Good use is made of bullet points and there are some flow charts. There are no pictures. The book is 15.5 cm × 23 cm which is too big for scrubs or white coat pockets; it is less likely to be used as a bedside reference than in quiet moments of repose. The content would also suit the latter use.

I would recommend this book to those in accident and emergency training to improve their knowledge of those generally less familiar corners of clinical activity emphasized in the speciality. The book will also add a welcome British perspective for those reading the larger North American reference texts. Others can use this book as a quick reference to broaden their knowledge of the work going on in accident and emergency departments, especially where it can impact on their own practice.

Tony Good
Royal Liverpool University Hospital
Liverpool
UK

Perioperative Medicine. Anthony Nicholls and Ian Wilson. Published by Oxford University Press, Oxford. Pp. 384; indexed; illustrated. price £19.95. ISBN 0 19-262975-1.

This concise book is aimed at trainees in the field of perioperative care, especially trainees in surgery and its subspecialities. The handbook is easy to understand and provides practical guidelines on the management of the patient in the perioperative period. It comprises four sections covering a spectrum of essential headings, for example risk management, preparing patients for elective and emergency surgery, cardiovascular disorders, and hypotension. Each section is divided into 10–20 chapters, representing a total of 52 chapters in 384 pages. Each chapter contains numerous references, which are either contemporary or landmark papers, and provide the reader with the option to research the subject in more detail.

The first section covers a wide range of general issues that can occur on surgical wards when patients with complex medical problems are being prepared for elective or emergency surgery. In the second section, the book provides pragmatic guidelines for the perioperative care of patients with common chronic medical disorders. Section 3 consists of short chapters on the diagnosis and management of various medical emergencies and complications in surgical patients, especially in the postoperative period. The last chapter of the book provides a table of the doses of prescribed perioperative drugs.

The authors have managed to cover most but not all relevant topics about medical and surgical problems in the perioperative period. In an attempt to produce a 'pocket size' book, the authors had to compromize between conciseness and completeness. In general, the chapters are well written and authors have indeed managed to design a real handbook, providing an easy source of quick information about daily bedside care on the word.

Due to the format, some important topics are missing, for example epistaxis and the management of acute pancreatitis. The topic of infection is hidden in different chapters. As this is a very important aspect of the management of the patient in the perioperative period, it would have been beneficial to give a more detailed discussion including more specific topics, for example meningitis or necrotizing fasciitis.

Additionally, the information provided in several chapters could usefully be displayed in the form of an algorithm. There are some algorithms provided in this book such as one for the intramuscular administration of opioids, cardiopulmonary resuscitation and the breathless patient, but their use should be extended.

Overall, the *Perioperative Medicine* handbook covers a wide range of relevant information, presented in a clear and practical manner. It provides comprehensive, practical guidance for routine diagnostic and therapeutic decisions. I think this is a very good book for trainees in the field of perioperative care for the immediate use at the bedside.

G. Marx
Liverpool
UK

Conscious Sedation. Jeanine P. Wiener-Kronish and Michael A. Gropper (editors). Published by Hanley & Belfus Inc., Philadelphia. Pp. 181; indexed. Price $37. ISBN 1-56053-413-3.

This is a small paperback book on the topic of conscious sedation. The authors have arranged it into 12 chapters and an index. A single author writes each chapter (with the exception of chapters 1 and 3). The chapter titles have been well chosen and reflect the use of conscious sedation. They include chapters on the pharmacology of conscious sedation as well as the reversal of conscious sedation. The book also includes a chapter on the 'Legal Issues in Conscious Sedation' and specific 'Nursing Issues in Conscious Sedation'.

This is a small book and it covers what is a small topic adequately. Any anaesthetist (or anesthesiologist in the USA where this book was written) will know most of what is written and will be very familiar with the use of conscious sedation in their daily practice. It is therefore a little disappointing that the pharmaceutical properties of the agents used for conscious sedation are repeated in detail by most of the different authors. The pharmaceutical properties of benzodiazepines, opioids and propofol are listed and explained in chapters 1, 3, 4, 5, 6, 7, 8 and 9 in a book that only has 12 chapters. It is a shame that the editors did not exercise their powers to coordinate the various authors so that there was not quite so much repetition of information. I was also a little disappointed that agents that are no longer used were given credence or coverage. Thus it was difficult to understand why etomidate was even mentioned in the chapter on sedation in ITU apart from to say that its use for ITU sedation has been banned and it does not have a product licence. The same chapter gives a full description of the use of ketamine in the ICU but starts this section with the sentence 'Recent national guidelines do not recommend the use of this agent as a sedative in the ICU'.

The chapter on 'Sedation in Pediatric Patients' was equally interesting. The author suggests that there should be one person whose sole responsibility is to both sedate and monitor the patient during the procedure (interestingly, this is not always mentioned as an absolute requirement in the various chapters on conscious sedation for other procedures). This person must be competent in sedating techniques and capable of managing the potential complications. Furthermore, the same chapter suggests that most of the sedative agents can cause anaesthesia when given in too large a dose. Given these two quite clear pieces of advice, I am not sure why the author does not come off the fence and state quite categorically that paediatric conscious sedation requires the presence of a trained paediatric anaesthetist. Who cares if this upsets the surgeons or the insurance companies, if it is safer for the children receiving the sedation then say so!

This book was clearly written for non-anaesthetists in North America. It encourages the idea that just about anybody can give conscious sedation. The pharmacokinetic principles are kept simple (a number of authors mention that fentanyl is short-acting, but none state that this is due to redistribution and not to metabolism or elimination). The take home messages are didactic and clearly aimed at the assistants to the person performing the procedure, rather than being of help to the person providing the conscious sedation. The drugs suggested are often not very popular in Europe and other parts of the world, and the drugs that are more popular in Europe and the rest of the world do not get full coverage. I cannot recommend this book to anaesthetists. It is repetitive and requires much more editorial control. Furthermore, any first-year trainee in anaesthesia will be familiar with all the drugs and techniques mentioned. Some of the recommendations do not put the safety of the patient first. Some of the drugs recommended do not have a product licence for the use that is suggested, and even North American guidelines do not recommend their use in some of the areas suggested.

R. M. Grounds
London
UK

Tumescent Local Anaesthesia. C. W. Hanke, B. Sommer and G. Sattler (editors). Published by Springer-Verlag, Heidelberg, New York. Pp. 211; illustrated. Price £30.50. ISBN 3-540-66544-7

I found myself rather intrigued on being presented with this book to review. Firstly, as a keen proponent of regional anaesthetic techniques, I had never encountered the term 'tumescent anaesthesia'. I wondered if I had missed out on a recent revolution in local anaesthesia and then I realized what a great mock *viva* question it would be for the trainees that afternoon.

The term derives from the Latin *tumescere*, meaning 'to swell', and the technique involves the delivery of industrial volumes (up to 6000 ml/adult) of dilute local anaesthetic into the subcutaneous tissues to provide widespread local anaesthesia. The application grew out of surgical techniques used for liposuction and the greatest application still appears to remain in this area. The technique has, however, been gaining popularity in the USA and Germany in particular, as an alternative to other anaesthetic techniques, regional or general, for a variety of other plastic surgical and superficial procedures. The book provides a useful background to the development of these techniques before covering other aspects in more detail.

In the first seciton, the book examines theoretical aspects including pharmacology, composition of the tumescent anaesthetic solutions, toxicology, adjuvant sedation and analgesic techniques, and a summary of potential advantages and disadvantages of the technique. The second section looks at the practical applications of the technique including descriptions of both manual and mechanical infiltration devices, as well as the cannulae pumps and other equipment required. The third section examines the various clinical indications in more detail. Much of the description focuses on plastic surgical procedures but other chapters address its use in breast surgery, varicose vein surgery and arthroscopy.

This is an interesting volume but I would have to say that the lack of a significant anaesthetic input leaves the text somewhat unbalanced. Many anaesthetists reading this text may express significant concerns over a number of areas and some of the more obvious contradictions apparent in different chapters. For example, in chapter 2 it states that changing from lidocaine to prilocaine (0.05–0.1%) allows even larger volumes of solution (3–5 litres) to be used. However, in chapter 3 it recommends doses of lidocaine up to at least 35 mg kg^{-1} but recommends restricting the dosage of prilocaine to 8–12 mg kg^{-1} due to concerns over methaemoglobinaemia. There is little mention of the safe duration for dosage administration and the book leaves a growing impression that more pharmacokinetic work still requires to be done. The chapter on pharmacology is fairly standard and well-written but more emphasis needs to be placed on the applied pharmacology and safety aspects of these techniques. The toxicology chapter is perhaps one of the most interesting as it draws our attention to potential fatal complications of the technique, the limitations of the current available evidence and the lack of many randomized-controlled trials.

The majority of the rest of the book concentrates on the practical application of these techniques and is aimed very much at the operator, emphasizing the hydrodissection effects, the lack of intraoperative bleeding and the postoperative analgesia. The technique for arthroscopy is very similar to conventional intra-articular block, with which many anaesthetists are familiar. By nature of the large number of authors in the practical chapters there tends to be a lot of repetition and also rather irritatingly, reiteration on more than a few occasions that the technique is 'without risk, unlike general anaesthesia', without presenting data to justify the claim.

On balance, I feel the book is aimed more as a practical guide for our surgical colleagues rather than being of use to anaesthetists. However, the concept is interesting, well worthy of further study, and will raise a few eyebrows in many anaesthetic departments.

D. M. Coventry
Dundee

Board Stiff Too—Preparing for the Anesthesia Orals (second edition). Christopher J. Gallagher, Steven E. Hill and David A. Lubarsky. Published by Butterworth-Heinemann, Boston. Pp. 390; indexed. Price £32.50. ISBN 0-7506-7157-2.

This is a book whose target audience is unashamedly those candidates about to take the American Board Oral Examinations in Anesthesiology, and therefore would at first glance appear to offer little to the reader not contemplating this ordeal. Steven Hill joins the two authors of the first edition, Christopher Gallagher and David Lubarsky, for this revised 2nd edition.

The book is divided into three sections. Part I, 'Driving School', consists of seven short chapters offering advice on the structure and conduct of the oral examinations, exam preparation, acquisition of knowledge, learning strategies and how to conduct oneself in front of the examiners. These chapters are amply illustrated by examples, no doubt drawn from personal experience, of the good *vs* the poor candidate. The style is informal and chatty echoing the advice of a paternalistic consultant to a trainee: practise aloud, practise aloud early, and practise often, classify or die, always answer the question etc.

Part II, 'Mechanics Manual', contains 14 short chapters covering key areas commonly covered in the oral examination. This pot-pourri includes chapters on anaesthesia and co-existing disease, for example patients with cardiovascular, respiratory and hepatic disease etc. presenting for surgery. Others deal with some specialized areas of anaesthetic practice such as neuroanaesthesia, the paediatric, the obstetric and the obese patient. But why has anaesthesia for cardiac, thoracic, vascular, and plastic surgery been omitted? In addition, there are chapters dealing with equipment, trauma, pain management, and blood and fluid replacement. Common perioperative anaesthetic scenarios are presented, and management strategies and the rationale for their use explained in a narrative and colloquial style. The advice offered is safe but often 'middle of the road' and only adequate for the candidate who wishes to pass but not to excel in the examination. The advice proffered would benefit greatly by the authors recommending a short list at the end of each chapter of selected further reading or references to established practice guidelines.

The final section of this book, approximately 60% of the total text, is devoted to practice questions and practice examinations in the format of the Board's examination. A series of case scenarios with accompanying questions relating to perioperative management are presented. The authors present a very personal view as to how these questions should be answered; indeed some of their management stretegies are at variance with my own views. They do, however, cover themselves in their final statement by recommending the book as a guide but not a text.

There is many an aspiring candidate for the FRCA or other postgraduate anaesthetic examination, who could learn from the advice offered in this text and benefit from working through the final practice question and answer section. I feel the majority however will, in the words of the authors, 'Slip the book back on the shelf, look around the medical bookstore ... Enjoy pizza and beer with the money they saved'.

J-P. van Besouw
London
UK

British Journal of Anaesthesia **87** (**1**): 164 (2001)

Erratum

*Effects of haemoglobin-based oxygen carrier Hemoglobin glutamer-200 (bovine) on intestinal perfusion and oxygenation in a canine hypovolaemia model (BJA 2001; **86:** 683–92)*

Systemic haemodynamic data (page 686, Results, Table 2), Ca_{O_2} (ml dl^{-1}), Sa_{O_2} (%) and $s\dot{V}_{O_2}$ (ml min^{-1}) data (page 687, Table 3), and systemic O_2 delivery data (page 687, Figure 2) were originally published by the authors in a recent study analysing systemic effects of Hemoglobin glutamer-200 (bovine) in the **same group** of animals (Driessen B, Jahr JS, Lurie F, Gunther RA. Inadequacy of low-volume resuscitation with hemoglobin-based oxygen carrier hemoglobin glutamer-200 (bovine) in canine hypovolemia. *Journal of Veterinary Pharmacology & Therapeutics* 2001; **24**: 61–71). These data were included to facilitate a comparison of the core data of the present investigation, in other words, data on intestinal perfusion and oxygenation, with those recorded in the systemic circulation.

The authors apologize for having omitted the above-mentioned reference in their *British Journal of Anaesthesia* article and for the confusion that the duplication of data might have caused among readers.

B. Driessen
J. S. Jahr
F. Lurie
S. M. Griffey
R. A. Gunther

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BJA

ABSTRACTS

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*The name of the author presenting the paper is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee*

VERBAL PRESENTATIONS

Effect of sustained lung inflation on pulmonary atelectasis during general anaesthesia in paediatric oncology patients

A. B. Lumb[1], K. Lapish[2]*, W. Ramsden[2]* and G. Lyons[1]

Departments of [1]Anaesthesia and [2]Radiology, St James's University Hospital, Leeds, UK

Areas of collapsed lung commonly occur during general anaesthesia for computerized tomography (CT) in children, and may mimic lung pathology.[1] Re-expansion of atelectasis in adults is difficult and achieved only by sustained inflation of the lungs to 40 cm H_2O for 5–15 s,[2] though inflation to 30 cm H_2O reduces the area of atelectasis by about half. Our aim was to determine if a similar manoeuvre to that described in adults was effective in children.

Eighteen children (age range 13–72 months) were studied, all of whom received general anaesthesia consisting of propofol or sevoflurane for induction, muscle relaxation with atracurium and maintenance using volatile agent in nitrous oxide and oxygen. Subjects' tracheas were intubated with an uncuffed tracheal tube, a leak at 20 cm H_2O inflation was confirmed and a throat pack was inserted. Children were then allocated randomly into two equal groups, the first of which received standard intermittent positive pressure ventilation (IPPV) with an expired tidal volume of 10 ml kg^{-1} and respiratory rate adjusted to achieve normocapnia. The second group had identical IPPV and, in addition, a series of three sustained lung inflations to an airway pressure of 30 cm H_2O for 10 s, 1 min apart, immediately before CT scanning. In both groups, data for spiral CT scans were acquired during manual inflation of the lungs to 20 cm H_2O (normally <15 s). The amount of atelectasis seen was measured in a single CT slice immediately cephalad to the right hemidiaphragm, by two staff who were unaware of the ventilatory technique used. Areas of atelectasis were identified by a senior radiologist and total pulmonary cross-sectional area and total area of atelectasis were calculated for each subject, following a technique described previously.[2] The amount of atelectasis present was expressed as a percentage of pulmonary cross-sectional area; the groups were compared by unpaired *t*-test using SPSS 9.0.

Overall, 12 subjects (67%) had some atelectasis on the CT scan. This is a similar incidence to previous reports, most of which involved data acquisition during expiration or throughout the respiratory cycle.[1 3 4] Mean (SD) percentage atelectasis was 3.40 (4.88)% in the group receiving standard IPPV and 1.79 (2.26)% in the sustained inflation group. The difference between the groups was not significant (P=0.38). It is possible that inflation to 40 cm H_2O would, as in adults, have re-expanded all atelectatic lung areas, but the anaesthetists responsible for the patients were concerned about the possibility of cardiovascular effects or even pulmonary barotrauma from this degree of increased intrathoracic pressure in small children.

In conclusion, this study of a small number of children did not demonstrate any advantage of acquiring CT scan data during sustained inspiration, whether or not this is preceded by a lung inflation manoeuvre similar to that used in adults to re-expand atelectasis. The small changes seen in our patients indicate that any potential clinical advantage to these techniques is small.

Keywords: complicatons, atelactasis; lung, atelactasis; anaesthesia, general; anaesthesia, paediatric

References

1 Damgaard-Pedersen K, Qvist T. *Ped Radiol* 1980; **9**: 145–8
2 Rothen HU, Neumann P, Berglund JE, *et al. Br J Anaesth* 1999; **82**: 551–6
3 Lam WWM, Chen PP, So NMC, Metreweli C. *Acta Radiol* 1998; **39**: 298–300
4 Sargent MA, McEachern AM, Jamieson DH, Kahwaji R. *Ped Radiol* 1999; **29**: 509–13

Can cerebral oxygen saturation be used as a transfusion trigger?

F. Torella*, S. L. Haynes*, A. J. Mortimer and C. N. McCollum*

Department of Surgery and Anaesthesia, South Manchester University Hospital, Nell Lane, West Didsbury, Manchester M20 2LR, UK

Increased oxygen extraction follows blood loss and anaemia.[1] Blood transfusion is given to restore oxygen delivery to the tissues and so should be administered only when this is deficient. To develop a transfusion trigger, the effect of blood transfusion on cerebral oxygenation was evaluated.

We monitored regional cerebral oxygen saturation (Cs_{O_2}) in 15 patients (11 men, age 23–83 yr) during 31 blood transfusions with reflectance near infrared spectroscopy (INVOS 4100). The oximeter sensor was placed on the left frontal area in 12 patients undergoing vascular surgery and three undergoing spinal surgery under general anaesthesia. Haemoglobin (Hb) concentration was measured by Hemocue before and after transfusion. Mean arterial pressure (MAP) from an indwelling arterial line, end-tidal carbon dioxide tension and pulse oximetry (Sa_{O_2}) were also monitored. Statistical analysis was by paired *t*-test and linear regression.

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The mean (SD) pretransfusion Hb concentration was 8.0 (1.34) g dl^{-1}, rising to 9.0 (1.98) g dl^{-1} after transfusion. Twenty-one transfusions were given when the Hb concentration fell below 8.5 g dl^{-1} (n=21), for unstable haemodynamics (n=3) or as routine reinfusion of autologous blood (n=7). When transfusions were given in response to low Hb concentration, Cs_{O_2} increased by a mean (95% confidence interval (CI)) of 6 (2.9–9.2)% (P=0.001). Blood given in the absence of an Hb transfusion trigger had little effect on Cs_{O_2}, with an increase of only 1 (–1.3 to 3.5)% (P=0.34). The increase in Cs_{O_2} correlated well with the increase in Hb concentration (R=0.73, P<0.001) and with the volume transfused (R=0.65, P<0.001). The correlations were particularly close if only transfusions in response to low Hb concentration were considered (R=0.79 and 0.77, respectively; P<0.001). Multiple linear regression confirmed a significant association between increases in Cs_{O_2} and Hb concentration (R=0.71, P<0.001) but no association between Cs_{O_2} and changes in Sa_{O_2} (P=0.3) or end-tidal carbon dioxide tension (P=0.3), MAP (P=0.08), or with the volume (P=0.08) or type (autologous or homologous) (P=1) of blood transfused.

Transfusion significantly improves cerebral oxygenation if given when the circulating Hb concentration falls below 8.5 g dL^{-1}. Cs_{O_2} may be developed into a transfusion trigger if further research confirms our findings.

Keywords: transfusion; brain, cerebral oximetry

Reference

1 Mathru M, Kleinman B, Blakeman B, *et al. Crit Care Med* 1991; **19**: 700–4

Induction of anaesthesia in the elderly day-case patient: double-blind comparison of propofol and sevoflurane

D. A. Kirkbride*, J. L. Parker, G. D. Williams* and D. J. Buggy

Department of Anaesthesia, University of Leicester and University Hospitals of Leicester NHS Trust, Leicester General Hospital, Leicester LE5 4PW, UK

Previous comparisons of propofol and sevoflurane have focused on a younger adult population (mean age <60 yr) and have yielded conflicting results in terms of haemodynamic stability and induction characteristics.[1–3] We compared induction of anaesthesia with propofol, incremental sevoflurane and 8% sevoflurane in an elderly day-case population in a randomized, double-blind trial.

Forty-five patients (mean (range) age 78 (72–85) yr) undergoing cystoscopy were allocated randomly to receive propofol (10 ml min^{-1} by infusion pump), incremental sevoflurane (starting at 1%, increasing by 1% every three breaths) or 8% sevoflurane. All patients received 50% nitrous oxide in oxygen via a facemask. Induction was defined as the moment when the patient dropped a hand-held 100 g weight. Observers were blind to group allocation because sevoflurane patients also received i.v. Intralipid, 10 ml min^{-1}, by infusion pump and vaporizers were concealed. Mean arterial pressure (MAP), heart rate (HR) and Sp_{O_2} were recorded for 6 min. Time to induction, apnoea, coughing, laryngeal spasm and involuntary movements were also documented.

The groups were comparable in terms of patient characteristics and baseline data. There was a significantly greater percentage reduction in MAP in the propofol group than in the sevoflurane groups (P = 0.004, ANOVA) (Fig. 1). HR was also lower (P=0.03, ANOVA) in the incremental sevoflurane group and Sp_{O_2} higher (P=0.04, ANOVA) in the 8% sevoflurane group than in the propofol group. Induction characteristics and patient willingness to undergo the same technique again were similar between the groups. Mean (SD) time to induction was similar in the 8% sevoflurane (97 (33) s) and propofol groups (106 (23) s), but longer with incremental sevoflurane (130 (33) s; P=0.03, Fisher's Exact). The dose of propofol in the propofol group was 180 (40) mg.

This study of anaesthetic induction in elderly day-case patients demonstrates that there is less hypotension in patients receiving sevoflurane than in those receiving propofol, with comparable induction characteristics, but incremental sevoflurane induction took predictably longer.

Keywords: anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane; age factors

References

1 Philip BK, Lombard LL, Roaf ER, *et al. Anesth Analg* 1999; **89**: 623–7
2 Fredman B, Nathanson MH, Smith I, *et al. Anesth Analg* 1995; **81**: 823–8
3 Thwaites A, Edmends S, Smith I. *Br J Anaesth* 1997; **78**: 356–61

Effects of remifentanil on plasma catecholamine response to laryngoscopy and endotracheal intubation

A. K. Gregg*, J. Strupish*, S. C. Rushman* and J. P. Thompson

University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK

Laryngoscopy and endotracheal intubation in anaesthetized subjects causes tachycardia and hypertension[1] and is associated with an increase in plasma catecholamine concentrations.[2] Beta-blockers attenuate the increases in heart rate and arterial pressure at laryngoscopy and intubation, but plasma catecholamine concentrations are not affected and may be increased.[3]

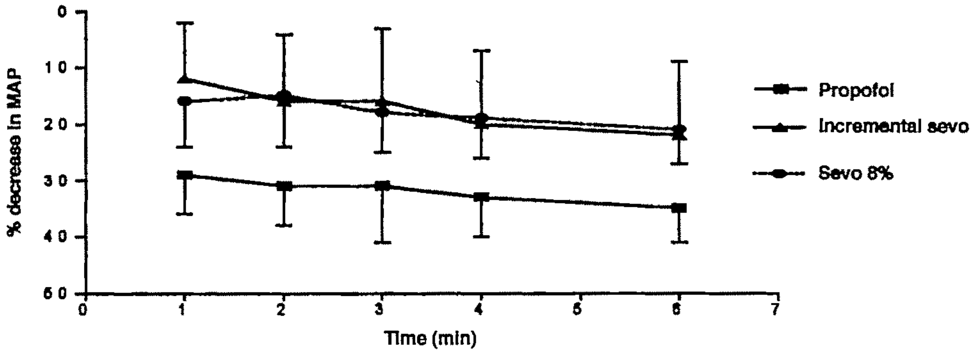

Fig 1 Percentage decrease in MAP over time.

Table 1 Heart rate, mean arterial pressure (MAP) and epinephrine and norepinephrine concentrations (mean (SD)). $^{*}P<0.05$ within group; $^{\dagger}P<0.05$ between groups; $^{\$}P=0.08$ between groups

	Group S ($n=20$)		Group R ($n=19$)	
	Before intubation	**After intubation**	**Before intubation**	**After intubation**
Heart rate (min^{-1})	79.6 (12.3)	104*† (14.8)	79.1 (13.1)	78.4 (19.6)
MAP (mm Hg)	78.3 (9.26)	99.1*† (15.9)	78.0 (8.44)	74.1 (16.4)
Norepi. (pmol ml^{-1})	3.09 (1.18)	3.96*$ (1.56)	2.82 (0.87)	2.84 (0.80)
Epinephrine (pmol ml^{-1})	0.26 (0.17)	0.32 (0.27)	0.30 (0.19)	0.30 (0.32)

Remifentanil attenuates the changes in heart rate and arterial pressure after intubation, but its effects on plasma catecholamine concentrations are unknown.

Forty ASA I–II female patients were allocated randomly to receive, in a double-blind manner, either remifentanil (0.5 μg kg^{-1} bolus over 30 s, followed by remifentanil 0.25 μg kg^{-1} min^{-1} infusion) (group R) or a saline placebo bolus and infusion (group S) at induction of anaesthesia. All patients received a standard general anaesthetic comprising propofol, rocuronium and 1% isoflurane in 66% nitrous oxide and 33% oxygen. Heart rate and arterial pressure were recorded at 1 min intervals. Blood was sampled from a pre-inserted venous cannula, before and after induction of anaesthesia, and 1, 3 and 5 min after intubation. Plasma epinephrine and norepinephrine concentrations were assayed using high performance liquid chromatography. Data were analysed using ANOVA for repeated measures.

One patient from group R was excluded because of failure to obtain blood samples. The groups were well matched for age, height, weight and view at laryngoscopy. Heart rate, arterial pressure and plasma norepinephrine concentrations increased significantly after intubation within group S ($P<0.05$), but not within group R (Table 1). There were no significant changes in epinephrine concentration in either group.

Laryngoscopy and endotracheal intubation were associated with increases in heart rate, arterial pressure and plasma norepinephrine concentrations in control patients. These responses were attenuated in patients who received remifentanil at induction of anaesthesia.

Keywords: analgesics opioid, remifentanil; blood, plasma, catecholamines

References

1 Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ. *Br J Anaesth* 1998; **80**: 467–9
2 Shribman AJ, Smith G, Achola KJ. *Br J Anaesth* 1987; **59**: 295–9
3 Maguire AM, Thompson JP, Guest C. *Anaesthesia*, in press.

Does i.v. clonidine enhance analgesia in daycase laparoscopic sterilization?

R. Vashisht[1]*, A. S. Laurence[1], J. E. Hall[2] and M. A. Bewley[1]

Departments of Anaesthetics, [1]Royal Preston Hospital and [2]North Tees Hospital, UK

Laparoscopic sterilization is commonly undertaken as a daycase procedure but is associated with significant post-operative pain. Pain may occur in the upper abdomen, lower abdomen, shoulder and back.[1] Visceral pain caused by tubal ligation is experienced in the lower abdomen. Clonidine, an α_2-adrenoceptor agonist, exhibits analgesic effects through both spinal and supraspinal sites. It has been used to supplement post-operative analgesia and is thought to be particularly effective for visceral pain.[2] Could a low dose, 1 μg kg^{-1} i.v., be effective without hypotensive effects in daycase patients?

Table 2 Post-operative morphine requirements, next-day pain scores and tablet consumption. *Mann Whitney. †On a scale of 0–100.

	Clonidine	Ketorolac	Significance*
Number of patients	10	11	
Morphine (mg)			
mean	12.1	5.3	
median (range)	10.5 (3–30)	5 (0–10)	$P<0.05$
Pain score† on next day, median (range)	42 (0–70)	35 (0–80)	NS
Clinical fall in arterial pressure after surgery	2/10	1/11	
Post-operative tablet consumption			
mean	7.2	3.2	
median (range)	7 (2–13)	3 (2–8)	

ASA grade I–II patients for daycase laparoscopic sterilization were assigned to one of two groups. Group I received clonidine 1 μg kg^{-1} i.v. and group II received ketorolac 30 mg (Table 2). Both clonidine and ketorolac were diluted in 50 ml of normal saline and infused over 10 min, immediately after induction. All patients received a standard anaesthetic using propofol, atracurium and a laryngeal mask and fentanyl 1.5 μg kg^{-1}. Anaesthesia was maintained with sevoflurane in nitrous oxide and oxygen. All patients were given oral ranitidine pre-operatively and ondansetron for antiemesis. Routine intra-operative monitoring was used. The need for any intervention to treat a clinically significant drop in arterial pressure during and after surgery was noted.

Patients were assessed immediately after surgery using a verbal pain score from 0 to 100. For a score above 40, increments of i.v. morphine were given as required. All patients were discharged with oral diclofenac and codeine/paracetamol. On the day after discharge they were telephoned to determine their pain since being at home and total tablet consumption.

We planned to recruit 60 patients, but there were early concerns regarding heavy requirements for post-operative morphine, so an interim analysis was undertaken. This revealed that the morphine requirement in the clonidine-treated group was significantly higher, so the decision was taken to terminate the study. We conclude that i.v. clonidine 1 μg kg^{-1} is unlikely to confer any analgesic advantage over ketorolac 30 mg in laparoscopy daycase patients.

Keywords: pain, post-operative; sympathetic nervous system, α-adrenergic agonists, clonidine

References

1 Alexander JL. *Br J Anaesth* 1997; **79**: 369–78
2 Bernard JM, Bourreli B, Hommeril JL, *et al. Acta Anaesthesiol Scand* 1991; **35**: 54–9

Comparison of 0.5% ropivacaine (5% glucose) with 0.5% bupivacaine (8% glucose) as spinal anaesthesia for elective surgery

J. B. Whiteside*, D. Burke* and J. A. W. Wildsmith

University Department of Anaesthesia, Ninewells Hospital, Dundee DD1 9SY, UK

Ropivacaine has been used little for spinal anaesthesia, but in solutions not containing supplements it has, like bupivacaine, resulted in very variable extent of block.[1] Previous work at this centre has demonstrated the efficacy of glucose-containing solutions of ropivacaine.[2] This study was designed to compare directly glucose-containing solutions of ropivacaine and bupivacaine.

Forty patients (ASA status I–II) undergoing spinal anaesthesia were allocated randomly to receive 3 ml of (i) ropivacaine 5 mg ml^{-1} in glucose 50 mg ml^{-1} or (ii) bupivacaine 5 mg ml^{-1} in glucose 80 mg ml^{-1}. This was injected over 10–15 s through a 25 standard wire gauge (swg) Whitacre needle ('port' facing laterally). After injection in the left lateral position, patients were turned supine for recording of sensory block (27 swg dental needle), motor block (Bromage scale 0–3), pulse rate and arterial pressure at 2, 5, 10, 15, 20, 25 and 30 min. Further assessments were made at 30 min intervals (surgery permitting) until complete block regression. Patients were contacted 24 h and 1 week after surgery to identify any late sequelae.

Table 3 Results of spinal block assessment in two groups of 20 patients, shown as median (range) unless otherwise indicated

	Bupivacaine	**Ropivacaine**	***P* value**
Sensory block			
Maximum level (dermatome)	T5 (T3–T11)	T7 (T4/5–T11)	0.0007
Time to onset at T10 (min)	2 (2–10)	5 (2–25)	0.0046
Duration at T10 (min)	118 (80–238)	57 (28–145)	0.001
Time to complete regression (min)	255 (150–240)	180 (120–270)	0.0001
Motor block			
Patients with grade 3 block, *n* (%)	20 (100)	14 (70)	0.02
Time to complete regression (min)	180 (120–210)	90 (60–180)	0.0001
Recovery			
Time to mobilize (min)	331 (219–475)	254 (151–359)	0.0019
Time to micturition (min)	341 (268–497)	276 (177–494)	0.01

The groups were similar in age, sex, height and weight. All blocks were adequate for the proposed surgery, but there were significant differences in sensory and motor characteristics between the groups (Table 3). Fourteen patients in the bupivacaine group and three in the ropivacaine group required treatment for hypotension (>30% decrease in systolic arterial pressure). One patient in each group developed a post-dural puncture headache, which settled spontaneously. There were no transient neurological symptoms in either group.

Ropivacaine in glucose 50 mg ml^{-1} can be used to provide reliable spinal anaesthesia of shorter duration, and with less hypotension, than bupivacaine. The recovery profile may be of interest, with more surgery being performed in the day-case setting.

Keywords: anaesthetic techniques, subarachnoid; anaesthetics local, ropivacaine; anaesthetics local, bupivacaine

References

1 van Kleef JW, Veering BT, Burm AGL. *Anesth Analg* 1994; **78**: 1125–30
2 Whiteside JB, Burke D, Wildsmith JAW. *Br J Anaesth* 2001; **86**: 241–4

Assessment of baseline arterial pressure before elective Caesarean section

D. G. Thomas* and P. Mowbray*

Dryburn Hospital, Durham, UK

Hypotension is an important complication of spinal anaesthesia for Caesarean section which can have adverse consequences for both mother and baby. Despite the importance of prompt control of maternal arterial pressure, the most appropriate method of determining the baseline has not been defined.[1] We investigated if arterial pressure measured immediately before operation predicted the normal arterial pressure.

Twenty-six fit healthy patients with a singleton pregnancy scheduled for elective Caesarean section at term participated in the study. The day before surgery, each patient rested for ⩾15 min in an armchair. Their arterial pressure was determined 15 times non-invasively (Cardiocap II); the mean of these values was considered to be the normal arterial pressure. Immediately before anaesthesia, arterial pressure was again measured six times (pre-spinal values), with the patient sitting, using the same device and

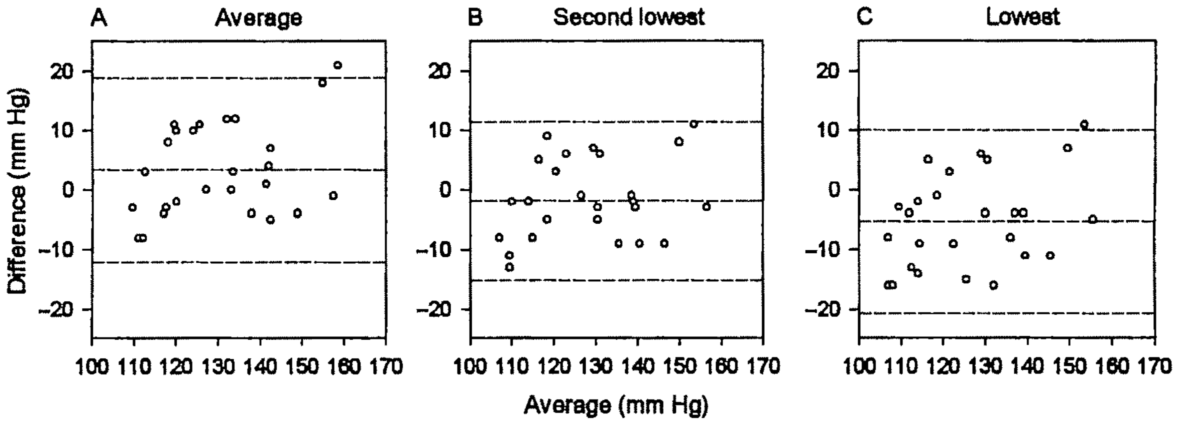

Fig 2 Difference between normal and pre-spinal systolic arterial pressure plotted against average of the two values. Horizontal lines are the 95% limits of agreement.

cuff. We then examined if the average or the extremes of these measurements could predict the normal arterial pressure. Values were compared using the 95% limits of agreement and paired *t*-testing (Figure 2).

The mean (SD) normal arterial pressure (128.8 (13.9) mm Hg) was less than the average pre-spinal arterial pressure (132.2 (16.6) mm Hg) (P=0.037) but greater than the lowest of the six pre-spinal pressure values (123.5 (16.7) mm Hg) (P=0.002). The second lowest systolic pressure measured before operation (127.0 (15.8) mm Hg) was not significantly different from the normal arterial pressure (P=0.187).

We conclude that the arterial pressure measured immediately before anaesthesia for Caesarean section may overestimate the normal arterial pressure, but by a small and probably clinically insignificant amount.

Keywords: arterial pressure; anaesthesia, obstetric

Reference

1 Kestin I. *Br J Anaesth* 1991; **66**: 596–607

Suprascapular nerve block for ipsilateral shoulder pain after thoracotomy with epidural analgesia: double-blind comparison of 0.5% bupivacaine and saline

N. M. Agnew*, C. N. H. Tan*, N. D. A. Scawn*, S. H. Pennefather*, G. N. Russell* and M. Chester*

The Cardiothoracic Centre, Liverpool NHS Trust, Thomas Drive, Liverpool L14 3PE, UK

Post-operative ipsilateral shoulder pain occurs in 75%[1] of patients who have received thoracic epidural analgesia during thoracotomy for lung resection. This complex pain is not treated effectively by conventional analgesics. The suprascapular nerve supplies the shoulder joint and has been implicated in the referred pain pathway from the diaphragmatic pleura via the phrenic nerve and in the transmission of pain originating from disorders of the shoulder joint. Relief of such pain has been achieved with stellate ganglion, interscalene brachial plexus[2] and phrenic nerve blocks, although respiratory depression secondary to diaphragmatic dysfunction can occur with all of these techniques. This double-blind randomized controlled study aimed to investigate if an ipsilateral suprascapular nerve block would be effective for post-thoracotomy shoulder pain.

In order to detect a 20% difference in pain scores with P<0.05 and power at 0.8, 15 patients needed to be recruited into each group. Thirty patients who complained of shoulder pain, despite effective thoracic epidural analgesia, were allocated randomly to receive a suprascapular nerve block with 10 ml of 0.5% bupivacaine or 10 ml of normal saline (control group). The anaesthetist was blinded to the solution used. Shoulder pain was assessed before nerve blockade (baseline) and 30 min and 1, 2, 3, 4 and 6 h after the injection using a visual analogue scale (VAS) and a five-point verbal ranking score (VRS) (Figure 3).

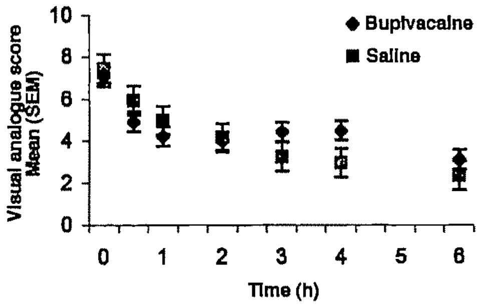

Fig 3 Visual analogue pain scores for the pain experienced by both groups 6 h after receiving the suprascapular nerve block

The incidence of shoulder pain before nerve block was 78%. There was no significant difference between the pain scores in the two groups in either VAS or VRS using repeated-measures analysis of variance.

Ipsilateral shoulder pain after thoracotomy in patients with an effective thoracic epidural is not adequately treated by suprascapular nerve blockade.

Keywords: anaesthetic techniques, regional, suprascapular nerve block; pain, post-operative

References

1 Burgess FW, Anderson DM, *et al. Anesthesiology* 1993; **78**: 365–8
2 Ng KP, Chow YF. *Anesth Intensive Care* 1997; **25**: 74–6

Effect of cocaine and lidocaine on beat frequency of human nasal cilia

A. Ng[1]*, B. Ayorinde[1]*, E. Pallett[1]*, J. Strupish[1]*, A. Banerjee[2]* and J. Thompson[1]

[1]*University Department of Anaesthesia and Pain Management and* [2]*Department of ENT Surgery, Leicester Royal Infirmary, Leicester LE1 5WW, UK*

Clearance of mucus in the respiratory tract is dependent on normal ciliary function. Although cocaine and lidocaine are commonly used during nasal surgery, their effects on ciliary function are not known. Ciliary beat frequency (CBF) has previously been used to quantify function[1 2]. Our aim was to investigate the effect of cocaine and lidocaine on CBF (Table 4).

Inferior turbinates from 10 patients were washed with medium 199 to remove blood and mucus. Discs of tissue were prepared using a punch biopsy and then placed in an antibiotic–antimycotic culture medium at 37°C. Using the transmitted light technique, baseline CBF was measured by placing a disc of tissue in a buffer solution (pH 7.4) at 37°C). The raw signal derived from the system was digitized to 16 bits and sampled at 100 Hz. Linear-phase digital bandpass filtering was used to reject unwanted frequencies and noise <1 Hz and >20 Hz. A 512-point fast Fourier

Table 4 Ciliary beat frequency

	Mean (95% confidence interval) CBF at concentration of						
	0 mM	0.3 mM	1 mM	3 mM	10 mM	20 mM	30 mM
Cocaine	13.1 (12.2–14.0)	13.0 (12.2–13.9)	12.8 (12.0–13.6)	12.3 (11.6–13.1)	11.4 (10.7–12.1)	3.3 (2.2–4.4)	0
Lidocaine	14.4 (13.8–14.9)	13.2 (12.6–13.9)	12.9 (12.1–13.6)	12.1 (11.5–12.7)	10.7 (10.0–11.4)	3.2 (2.3–4.1)	0

transform (FFT) was used to obtain CBF in real time to an accuracy of 0.2 Hz. The frequency component in the FFT spectrum with the largest amplitude was the recorded CBF value. Discs of tissue were then exposed to cocaine at concentrations of 0.3, 1, 3, 10, 20 and 30 mM, at pH 7.4 and 37°C. After 20 min at each concentration, CBF was measured from six healthy parts of the disc. The procedure was repeated with the same concentrations of lidocaine, using different discs of tissue.

Nasal CBF was reduced by increasing concentrations of cocaine and lidocaine. *In vitro*, human nasal ciliary function is impaired by clinically relevant concentrations of cocaine or lidocaine.

Keywords: anaesthetics local, cocaine; anaesthetics local, lidocaine; nose, cilia

References

1 Raphael JH, Strupish J, Selwyn DA, *et al. Br J Anaesth* 1996; **76**: 854–9
2 Hann HCL, Hall AP, Rapheal JH, Langton JA. *Int Care Med* 1998; **24**: 791–4

Interleukin-10 and tumour necrosis factor α concentrations and red cell hypochromasia in critical illness

N. Collighan*, S. D. Murdoch and M. C. Bellamy

Intensive Care Unit, St James's University Hospital, Leeds, UK

Hypochromasia is present when >10% of red blood cells contain <27 pg of haemoglobin. In the critically ill patient, hypochromasia is an acute event occurring in the 24 h before ITU admissions for sepsis. It is associated with an increased length of stay and duration of organ failure on the ITU.[1] This is due not to functional iron deficiency but to an acute increase in red cell size.[2] This change is related to an increase in overall cell ATP content probably secondary to impairment in intracellular ATPases.[3] The aim of this study was to determine if these changes are related to cytokine activation. We chose tumour necrosis factor α (TNF-α) as a candidate pro-inflammatory cytokine and interleukin 10 (IL-10) as a candidate anti-inflammatory cytokine.

Over a period of 1 month, all adult patients admitted to our ITU with signs of sepsis were recruited. Any patient who had received a large blood transfusion (>8 units), had a haematological malignancy or was in chronic renal failure was excluded. Blood samples were taken from each patient on days 1 and 2 and all routine blood results were noted, as were Apache II score on admission and length of stay. Percentage red cell hypochromasia was measured using a full blood count sample on a Bayer Advia auto-analyser. A clotted sample was centrifuged at 2000 r.p.m. for 20 min and the serum was frozen to allow later analysis. ATP concentrations in the same samples were measured as described previously.[3] Standard enzyme-linked immunosorbent assay (ELISA) kits were used to quantify TNF-α and IL-10. After analysis, we had 17 complete sets of results for days 1 and 2. Cytokine and red cell ATP concentrations were compared between patients with and without hypochromasia. Correlations were calculated between cytokine serum concentrations and percentage hypochromasia. Day 1 results are shown in Table 5.

Table 5 Interleukin 10 (IL-10), tumour necrosis factor α (TNF-α) and red blood cell (RBC) ATP concentrations in patients with and without hypochromasia; data are shown as median (range) for IL-10 and TNF-α, mean (SD) for RBC

	No hypochromasia (*n* = 12)	**Hypochromasia** (*n* = 5)	r^2	*P*
[IL-10], pg ml^{-1}	47.86 (0–500)	27.45 (0–500)	0.0479	0.4152
[TNF-α], pg ml^{-1}	28.84 (0–83.18)	30.15 (0–36.31)	0.136	0.5028
RBC [ATP], mol 100 ml^{-1}	49.9 (7.82)	66.6 (5.43)	0.626	0.0006

No significant relationship was found between hypochromasia and either IL-10 or TNF-α concentration. As previously described, no relationship was found when comparing hypochromasia with lactate concentration, Apache II scores on admission, C-reactive protein, whether inotropes were required or white cell count. We confirmed our previous data showing a significant relationship (P<0.0006) between hypochromasia and ATP concentration. IL-10 and TNF-α concentrations appear to be unrelated to the development of ATPase impairment and hypochromasia in the critically ill patient.

Keywords: intensive care; blood, erythrocytes, hypochromasia

References

1 Bellamy MC, Gedney JA. *Lancet* 1998; **352**: 1903
2 Murdoch SD, O'Malley C, Bellamy MC. *Br J Anaesth* 2000; **85**: 156P
3 Murdoch SD, Collighan N, Bellamy MC. *Br J Anaesth* 2001; In press

Polymorphism of the manganese superoxide dismutase gene *SOD2*

N. E. ElSakka*, P. R. Lowe*, H. F. Galley and N. R. Webster

Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, UK

Mitochondria are targets for oxidative damage and mitochondrial dysfunction, as shown in animal models and in studies of patients with sepsis. The manganese isoform of the antioxidant enzyme, superoxide dismutase (MnSOD), protects mitochondria against both oxidant stress and consequent damage. Genetic variation in the gene for MnSOD *SOD2* may dictate susceptibility of individuals to mitochondrial oxidant damage. A functional polymorphism of the MnSOD gene has been described where a point mutation encoding the mitochondrial targeting sequence results in cytosine being replaced with thymine, causing an amino acid change from alanine to valine. This change alters the secondary structure of the protein, affecting mitochondrial transport of MnSOD and hence enzyme activity. The frequency of the polymorophism has been described in the USA, Germany and Japan, but has not been reported in a UK population. The aim of the present study was to establish the frequency of this polymorphic marker in healthy UK subjects, before studying patients with sepsis.

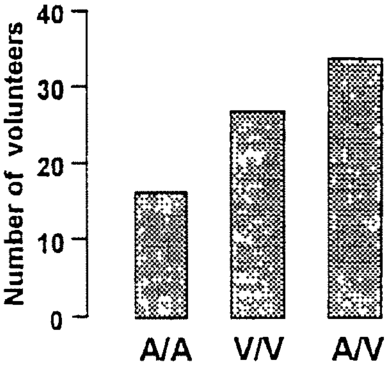

Fig 4 Analysis of genotypes revealed that 17 (21%) of the subjects were homozygous for alanine, 28 (35%) homozygous for valine and 35 (44%) heterozygous.

In this interim analysis we present the results obtained from the first 80 consecutive subjects (55 females and 25 males) aged 21–61 yr. Genomic DNA was extracted from EDTA-treated blood using a BACC3 DNA isolation kit (Nuclean). The polymerase chain reaction (PCR) was used to amplify the area of DNA containing the MnSOD gene. Restriction fragment length polymorphism analysis was performed using the restriction enzyme *Bsa*WI, which cuts the DNA fragment when the codon encoding the valine substitution, GTT, is present, yielding two DNA fragments of 87 and 159 bp. The wild-type sequence, GCT, is unaffected so a single uncut DNA fragment of 246 bp is seen. Agarose gel electrophoresis with ethidium bromide was used to separate and visualize the digested PCR product. Subjects were assigned to one of three possible genotypes: homozygous for the wild-type allele (A/A), homozygous for the polymorphism (V/V) or heterozygous (A/V) (Figure 4).

The interim data show that a sizeable percentage of the population carry the polymorphism, which has been associated with altered intra-mitochondrial transport and activity of MnSOD. Further studies are needed to demonstrate any significant differences in outcome from sepsis and multiorgan failure associated with this polymorphism.

Keywords: enzymes, manganese superoxide dismutase; genetic factors

Circulating concentrations of vascular endothelial growth factor after cardiopulmonary bypass

P. Townsend*, H. F. Galley, R. L. Carmichael and N. R. Webster

Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, UK

A marked systemic inflammatory response occurs after cardiopulmonary bypass. Vascular endothelial growth factor (VEGF) is an angiogenic factor produced by a variety of cells, including cardiac myocytes, endothelial cells and macrophages, with specific receptors localized on the endothelium. Although VEGF may have beneficial effects in the setting of cardiac surgery, it also contributes to the inflammatory response through release of adhesion molecules, metalloproteinases and nitric oxide, via the transcription factor AP-1. The gene for VEGF contains sheer stress core elements, and the regulatory protein complex, hypoxia inducible factor-1, stabilizes VEGF mRNA, resulting in rapid increases in VEGF protein on exposure to hypoxia. Both hypoxia and sheer stress occur during cardiopulmonary bypass. Release of VEGF increases in rat cardiac myocytes exposed to hypoxia. We therefore measured circulating VEGF concentrations in 145 patients undergoing cardiopulmonary bypass.

Patients undergoing elective cardiac surgery involving cardiopulmonary bypass were recruited. Blood samples were obtained before bypass and 3 and 24 h after bypass. Samples were immediately centrifuged and frozen at –80°C. Circulating VEGF concentrations were measured using enzyme immunoassay. Data are expressed as median (range) and were assessed using Friedman analysis of variance with Wilcoxon signed ranks *post hoc* testing for paired data.

VEGF was detectable at all times. Analysis of variance showed a significant change over the three time points ($P<0.001$). In all patients, VEGF concentrations increased after bypass; the median (range) circulating VEGF concentration was 54.8 (1.9–233.9) pg ml^{-1} before bypass, 52.0 (1.4–160.3) pg ml^{-1} 3 h after bypass and 84.1 (10.4–213.9) pg ml^{-1} 24 h after bypass. Concentrations 24 h after bypass were significantly higher than those before bypass or 3 h after bypass ($P<0.001$; Wilcoxon signed ranks test).

VEGF concentrations are increased 24 h after cardiopulmonary bypass, consistent with mRNA production and *de novo* protein synthesis. VEGF stimulates endothelial cell proliferation, inhibits intimal hyperplasia and may protect against apoptosis. However, it also has a role in the inflammatory response and stimulates the expression of adhesion molecules and metalloproteinases. Further studies are needed to determine the complex interactions of increased VEGF release after cardiac surgery.

Acknowledgement

We are grateful to the Scottish Hospitals Endowment Research Trust and the Intensive Care Society for financial support.

Keywords: surgery, cardiovascular

Modulation of synaptic activity in mammalian neurones by the sleep hormone *cis*-9,10-octadecenoamide

L. Coyne*, A. C. Errington* and G. Lees

Institute of Pharmacy, School of Sciences, University of Sunderland, Darwin Building, Wharncliffe Street, Sunderland SR1 3SD, UK

The sleep hormone *cis*-9,10-octadecenoamide (cOA or 'oleamide') modulates central nervous system γ-aminobutyric acid (GABA)$_A$ receptors[1] and inhibitory synaptic currents. It suppresses burst firing[1] secondary to state-dependent block of voltage-gated sodium channels[2]. Both of these ion channels are frequently cited as important cellular targets for anaesthetics.[3] In this study we have characterized the effects of cOA on synaptic signalling in cultured neurones from rat cortex.

Culture techniques and saline composition were as described previously.[1] Whole-cell patch clamping was performed at 22–24°C. All solutions contained 0.1% bovine serum albumin and 0.1% dimethylsulphoxide. Data were analysed (Spike 2 software from CED Ltd UK; Prism 3 from Graphpad CA, USA; and WinWCP, University of Strathclyde) using paired, two-tailed Student's *t*-tests. *P* values of <0.05 were considered significant.

In physiological saline at a holding potential of –45 mV, 20 µM cOA significantly reduced the incidence of spontaneous excitatory synaptic events ($P=0.004$, $n=4$). The sampled events were averaged. cOA did significantly alter the mean amplitude ($P=0.013$, $n=4$). Closer examination of spontaneous events revealed that many pre-synaptic cells exhibited repetitive firing and that cOA suppressed the regenerative activity but not the primary spikes.

In 200 nM tetrodotoxin and 10 µM picrotoxin, we isolated glutamatergic miniature excitatory post-synaptic potentials (mEPSCs) at a holding potential of –70 mV. cOA at 20 µM did not significantly alter the amplitude or decay kinetics (time for 50% or 90% decay) of averaged mEPSCs ($n=6$).

We conclude that cOA exerts a predominantly pre-synaptic effect on the cultured circuits. The depression of evoked synaptic events is similar to the effects of isoflurane in our laboratory and glutamate receptors are relatively insensitive to modulation by a variety of anaesthetics. Oleamide may be an endogenous ligand for drug recognition sites in the CNS.

Acknowledgements

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Keywords: hormones, oleamide; brain, synaptic signalling

References

1 Verdon B, Zheng J, Nicholson RA, Ganellin CR, Lees G. *Br J Pharmacol* 2000; **129**: 283–90
2 Nicholson RA, Zheng J, Ganellin CR, Verdon B, Lees G. *Anesthesiology* 2001; **94**: 120–28
3 Lees G. *Br J Anaesth* 1998; **81**: 491–3

Oleamide: a putative endogenous ligand for anaesthetic receptor sites

D. P. Laws[1]* and G. Lees[2]

[1]Sunderland Royal Hospital, Kayll Road, Sunderland, SR4 7TP; [2]Institute of Pharmacy and Chemistry, School of Sciences, University of Sunderland, Wharncliffe Street, Sunderland SR1 3SD, UK

The state of physiological sleep is clearly distinct from that of clinical anaesthesia. However, the two states may share common molecular pathways. We have compared the actions of *cis*-9,10-octadecenoamide (oleamide), a hypnogenic compound that accumulates in cerebrospinal fluid on sleep deprivation,[1] with that of the barbiturate, pentobarbital, using electrophysiological studies in primary rat brain cortical cultures.

Standard physiological salines were used (extracellular saline contained 0.1% bovine serum albumin and 0.1% dimethylsulphoxide).[2] Cell cultures were used after 14–35 days *in vitro.*[2] Spontaneous synaptic activity and γ-aminobutyric acid (GABA)$_A$ receptor function were explored using the whole-cell patch-clamp technique at 22–24°C. Depressant compounds were either superfused on to cultured cells or applied rapidly (together with exogenous GABA) via a Y-tube. Results are expressed as mean (SD). Paired or unpaired two-tailed *t*-tests were used as appropriate. $P<0.05$ was considered significant.

The incidence of spontaneous synaptic currents diminished with application of each compound, indicating a possible common site of action upon polysynaptic pathways or pre-synaptic cells. Oleamide (20 μM) and pentobarbital (100 μM) reversibly enhanced currents evoked by GABA at 3.2 μM. Modulation (expressed as a percentage of the control chloride current) was 134 (11.0)% and 141.5 (24.6)%, respectively. The slow onset kinetics of oleamide contrast greatly with those of pentobarbital. Pentobarbital rapidly achieved maximal modulation (within a 2 s agonist pulse), but oleamide was perfused for 250 (22.4) s (n=6) before the modulatory action reached steady state.

The enhancement of GABA (3.2 μM)-induced currents by 100 μM pentobarbital (201.2 (20.0)%) was not further enhanced or inhibited by superfusion of 20 μM oleamide (205.7 (20.7)%); P=0.54, n=6).

The comparable modulatory efficacy shown by oleamide and pentobarbital and the lack of additivity suggest a common pathway of action. However, the divergent onset kinetics, which may reflect physicochemical differences, are not consistent with this simple interpretation. The fatty acid amides may be endogenous ligands for anaesthetic recognition sites in mammalian brain.[2 3]

Acknowledgements

Thanks to The Wellcome Trust (for equipment support) and to Adam Errington for technical support (for cell cultures).

Keywords: hormones, oleamide; receptors, GABA$_A$

References

1 Cravatt BF, Prosperogarcia O, Siuzdak G, *et al. Science* 1995; **268**: 1506–9
2 Verdon B, Zheng J, Nicholson RA, Ganellin CR, Lees G. *Br J Pharmacol* 2000; **129**: 283–90
3 Nicholson RA, Zheng J, Ganellin CR, Verdon B, Lees G. *Anesthesiology* 2001; **94**: 120–28

Terminal complement complex in porcine septic shock with capillary leak syndrome

G. Marx[1]*, M. Cobas Meyer[2]*, T. Schuerholz[2]*, B. Vangerow[2]*, J. Schmittko[3]*, K.F. Gratz[4]*, M. Winkler[3]*, H. Rueckoldt[2]* and M. Leuwer[1]

[1]University Department of Anaesthesia, University of Liverpool, UK; Departments of [2]Anaesthesia, [3]Viceral and Transplant Surgery and [4]Nuclear Medicine, Hannover Medical School, Germany

It has been suggested that the reduced levels of complement proteins seen in sepsis with capillary leak syndrome (CLS) may partly be explained by haemodilution and leakage of proteins.[1] The aim of this prospective randomized, controlled animal laboratory study was to monitor complement activation by investigating intravascular levels of terminal complement complex (TCC), as well as its extravascular deposition in an animal model of septic shock with capillary leak.

Ten fasted, anaesthetized, mechanically ventilated and multi-catheterized pigs (mean (SD) weight 20.6 (1.3) kg) were investigated over a period of 8 h. In five animals in the study group, sepsis was induced by faecal peritonitis (1 g faeces kg body weight^{-1}); this group was compared with the control group (n=5). The animals received 6% hydroxyethyl starch 200/0.5 to maintain a central venous pressure of 12 mm Hg. Plasma levels of TCC were measured by a double antibody enzyme immunoassay using the neoepitope-specific monoclonal antibody aE11 as catching antibody.[2] *Post mortem* immunohistological examination of renal specimens was performed to detect TCC deposition. CLS was calculated by albumin escape rate (AER) using technetium 99m-labelled human serum albumin. In order to assess haemodilution, the haematocrit (Hct) was determined. After verifying normal data distribution (skewness <1.5), Student's *t*-test was performed by rank-ordered stepwise testing.[3] P values of <0.05 were considered significant. Data are presented as mean (SD).

Septic animals showed marked renal deposition of TCC, whereas no deposition of TCC occurred in control animals. Other results are shown in Table 6.

Plasma levels of TCC decreased during the study period in both groups. In control animals this may have been caused by

Table 6 Deposition of terminal complement complex (TCC), albumin escape rate (AER) and haematocrit (Hct) in pigs in which sepsis was introduced ('study group'; n=5) and control animals (n=5). *$P<0.05$ compared with baseline; $^{\#}P<0.05$ for intergroup comparison

	Baseline		**4 h after sepsis induction**		**8 h after sepsis induction**	
	Study group	**Control group**	**Study group**	**Control group**	**Study group**	**Control group**
TCC (%)	104 (40)	118 (37)	22 (29)*	58 (11)*	16 (31)*	20 (22)*
AER (%)		39 (16)*,$^{\#}$	5 (5)	52 (26)*,$^{\#}$	3 (10)	
Hct (%)	29 (1)	29 (2)	30 (5)	25 (3)*	29 (3)	26 (1)*

haemodilution. In septic animals this finding was accompanied by a marked deposition of TCC in the kidney. As AER was significantly higher in septic animals, capillary loss of TCC into organ tissue may be the explanation. We conclude that in septic shock with capillary leak syndrome, the plasma level of TCC alone may not be a reliable indicator of complement activation.

Keywords: immune response, complement membrane attack complex; blood, capillary leak syndrome

References

1 Nuijens JH, Huijbregts CC, Eerenberg-Belmer AJ, *et al. Blood* 1988, **72**: 1841–8

2 Mollnes TE, Redl H, Hogasen K, *et al. Clin Exp Immunol* 1993; **91**: 295–300

3 Marcus R, Peritz E, Gabriel KP. *Biometrika* 1976; **63**: 655–60

Acute phase response (interleukin 6 and complement-1 inhibitor) to surgery in patients with oropharyngeal carcinoma

M. Cobas Meyer[1]*, H. Rueckoldt[1]*, G. Marx[2]*, T. Schuerholz[1]*, B. Vangerow[1]*, J. Ahrens[1]*, R. Appiah[1]* and M. Leuwer[2]

[1]*Department of Anaesthesia, Hannover Medical School, Germany;* [2]*University Department of Anaesthesia, University of Liverpool, UK*

In patients with oropharyngeal carcinoma (OPC), persistently elevated serum concentrations of interleukin 6 (IL-6) have been reported, indicating a chronic inflammatory state.[1] In addition, it has been suggested that, in turn, chronic inflammation may alter the acute phase response (APR).[2] In a prospective clinical observation study, we examined two aspects of the APR, IL-6 and complement-1 inhibitor (C1-Inh) in patients with OPC who underwent tumour resection.

The OPC group included eight patients with OPC without metastasis and the control group included six patients with non-malignant head and neck diseases. All underwent major head and neck surgery. IL-6 was measured using Medgenix IL-6 45 min enzyme amplified sensitivity immunoassay, C1-Inh activity using a Berichrom C1 inactivator and C1-Inh protein concentration using NOR-Partigen. To compare pre-operative values with those at ICU admission and on the day after surgery, a Friedman test with *post hoc* Wilcoxon test was performed. Data are presented as median (range). $P<0.05$ was considered significant.

The groups were comparable with respect to patient characteristics, duration of operation, intra-operative blood loss, volume resuscitation, duration of ICU stay and haematocrit (data not shown). Peri-operative IL-6 and C1-Inh levels are shown in Table 7.

Table 7 Median (range) concentration of interleukin 6 (IL-6) and activity and concentration of complement-1 inhibitor (C1-Inh). $^*P<0.05$ compared with pre-operative values (Friedman's test with *post-hoc* Wilcoxon)

	Before surgery	At ICU admission	On day after surgery
IL-6 (pg ml^{-1})			
oropharyngeal carcinoma	0 (0–194)	319 (80–1669)*	184 (50–419)*
control	0 (0–234)	75 (33–267)	193 (26–244)
C1-Inh activity (%)			
oropharyngeal carcinoma	109 (80–141)	82 (59–105)*	105 (72–145)
control	100 (71–120)	100 (84–139)	93 (76–118)
C1-Inh protein (%)			
oropharyngeal carcinoma	105 (44–163)	86 (60–110)	105 (68–152)
control	103 (60–120)	92 (73–130)	89 (56–130)

We did not detect persistently elevated IL-6 concentrations in patients with OPC without metastasis. However, the immediate IL-6 response to surgery was more marked in these patients. Surprisingly, although IL-6 is a potent stimulator of hepatic acute phase protein synthesis, C1-Inh activity was decreased initially in these patients. Thus, the APR may be altered in patients with OPC, even if IL-6 concentrations are not elevated before surgery.

Keywords: immune response, acute phase response; cancer, carcinoma

References

1 Gallo O, Gori AM, Attanasio M, *et al. Br J Cancer* 1992; **65**: 479–80

2 Biró L, Domján G, Falus A, *et al. Eur J Clin Invest* 1998; **28**: 679–86

Effect of shock and controlled fluid resuscitation on extravascular lung water content in a combined trauma–hypovolaemic shock model

M. Nirmalan[1], T. Willard[1], M. O. Columb[2], D. J. Edwards[1] and R. A. Little[1]*

[1]*MRC Trauma Group, University of Manchester, Oxford Road, Manchester M13 9PT;* [2]*Intensive Care Unit, South Manchester University Hospitals, Manchester M20 2LR, UK*

The acute effects of shock on pulmonary function and extravascular lung water (EVLW) content are poorly described. This study used the dual dye-dilution method (Cold Z021; Pulsion) to determine EVLW content[1] in a model of shock based on cardiac output, arterial pressure, blood lactate concentration and mixed venous oxygen saturation. Anaesthetized large white pigs (21–35 kg) were allocated randomly to a control group (n=9) and two shock groups (crystalloid, n=10; colloid, n=10). The pigs were maintained in shock for 1 h and then resuscitated. EVLW content, dynamic lung compliance and venous admixture (Q_s/Q_t) were determined at specific time points. Data were analysed using analysis of covariance (ANCOVA) and general linear model (GLM) procedures (NCSS 2000, SPSS 9.0) with $P<0.05$ considered significant.

No significant changes in Q_s/Q_t, compliance or EVLW were seen with respect to the type of fluid resuscitation. Using ANCOVA, serum lactate concentration was found to be the most significant (P=0.023) of the shock end-points influencing EVLW. *Post hoc* analysis based on blood lactate concentrations (Figure 5)

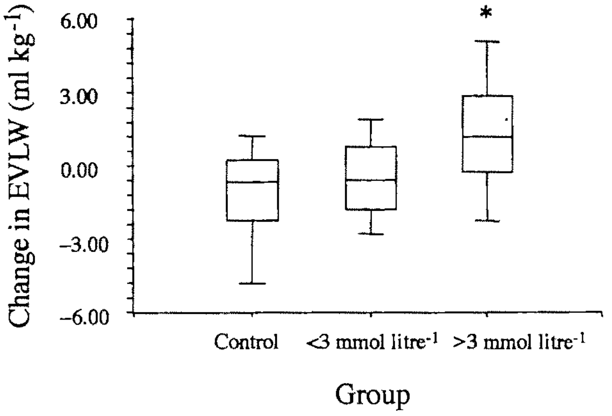

Fig 5 Changes in lung water with severity of shock. Box-and-whisker plots show 2.5, 25, 50, 75 and 97.5 percentiles. *Significantly different from control (P=0.013).

showed a significant (F=4.1, P=0.029) increase in EVLW in animals with higher lactate concentrations during the shock phase.

The study provides important preliminary evidence that pulmonary capillary damage resulting in increased EVLW content may occur in early shock in the absence of fluid overload. The increase was related to the severity of shock rather than the type of resuscitation fluid. Further studies performed over longer periods are indicated to characterize the nature of pulmonary damage and the role of resuscitation fluids in shock.

Acknowledgement

The study was funded by the MRC and Maelor Pharmaceuticals Ltd.

Keywords: shock; lung, water; lung, function

Reference

1 Lewis FR, Elings VB, Hill SL, Christensen JM. *Ann NY Acad Sci* 1982; **384**: 394–411

Analgesic effect of gabapentin premedication in laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial

A. K. Gregg*, S. Francis, P. Sharpe and D. J. Rowbotham

University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK

Gabapentin is an anticonvulsant drug that provides symptomatic relief in certain chronic pain syndromes.[1] In animal models, gabapentin reduces acute nociceptive pain.[2 3] The mechanism by which gabapentin produces analgesia is uncertain; however, closure of voltage-gated calcium channels, increased concentrations of γ-aminobutyric acid (GABA) without direct binding to the GABA receptor,[1] and reduced glutamate transmission[4] have all been suggested. A side effect of gabapentin is somnolence, creating a potential interaction with the induction of anaesthesia.

Forty ASA I–II patients, aged 18–65 yr, undergoing laparoscopic cholecystectomy, were premedicated with gabapentin 300 mg or placebo, in a randomized, double-blind manner. A power calculation was performed, based on reducing the need for supplemental analgesia within 6 h from 70% to 30%, assuming 5% α and 20% β errors. Anaesthesia, analgesia and surgical technique were all standardized. The time to initial request for post-operative rescue analgesia was recorded. Visual analogue pain scores, categorical pain scores and sedation scores were recorded hourly for 6 h.

The gabapentin and placebo groups were well matched for age and sex distribution.

There were no significant differences in any of the pain or sedation scores at any time (P>0.05, ANOVA). There were no reported adverse effects in either group (Table 8).

Table 8 Analgesia in patients undergoing laparoscopic cholecystectomy, premedicated with gabapentin 300 mg or placebo

	Gabapentin	Placebo	*P* value	95% CI of difference
Number in group	19	20	–	–
Age (years) mean (range)	47 (20–63)	46 (24–68)	0.74 (*t*-test)	–8.3 to 8.1
Propofol dose (mg) mean (SD)	152 (22)	160 (23)	0.24 (*t*-test)	–6 to 23
Time to initial analgesia (min), median (range)	360 (40–360)	275 (15–360)	0.23 (Mann–Whitney)	0 to 140
Supplemental analgesia	8/19 (42%)	13/20 (65%)	0.20 (Fisher)	–47% to 17%

Premedication with gabapentin 300 mg 1 h before laparoscopic cholecystectomy has no significant effect on acute post-operative pain or induction dose of propofol. Further studies, possibly with increased doses of gabapentin or with gabapentin continued into the post-operative period, are required.

Keywords: anticonvulsant, gabapentin; pain

References

1 Mao J, Chen LL. *Anesth Analg* 2000; **91**: 680–7
2 Cheng JK, Pan HL, Eisenach JC. *Anaesthesiology* 2000; **92**: 1126–31
3 Field MJ, Holloman EF, McCleary S, et al. *J Pharmacol Exp Ther* 1997; **282**: 1242–6
4 McLean MJ. *Epilepsia* 1999; **40**: S39–50

Bench study of the changes in estimated perfusion pressure and zero-flow pressure as assessed using Doppler ultrasonography

R. P. Mahajan, S. M. Hancock* and L. Athanassiou*

University Department of Anaesthesia and Intensive Care, Queen's Medical Centre, Nottingham, UK

A non-invasive method of estimating cerebral perfusion pressure using transcranial Doppler ultrasonography has been described.[1] Its reliability in assessing moderate changes in the perfusion pressure (PP) and/or zero-flow pressure (ZFP) is not known. We aimed to address this issue.

A bench pulsatile flow model was constructed using artificial vessels and perfusion media. This included a computer-controlled pump capable of generating flow waves of predetermined characteristics. The circulatory circuit incorporated a *Windkessel*, a bypass limb with variable resistance and an insonated limb with a variable peripheral resistance. The flow velocity (FV) profile of the internal carotid artery was simulated. Pulse rate and total flow were kept constant. The flow through the insonated limb and the driving pressure were altered by changing the resistances of the insonated and the bypass limbs; eight configurations were studied. At each configuration of resistances, the PP in the insonated limb was

Table 9 Median (25%, 75% quartiles) flow velocity (FV), perfusion pressure (PP), estimated perfusion pressure (EPP) and zero-flow pressure (ZFP) at different downstream pressures

	Downstream pressure (mm Hg)			
	41 (*n*=8)	**25 (*n*=8)**	**12 (*n*=8)**	**Kruskal–Wallis *P***
FV_{mean} (KHz)	2.7 (2.0, 3.1)	3.3 (2.8, 3.6)	3.8 (3.0, 3.9)	<0.01
PP (mm,Hg)	35 (29, 45)	48 (41, 57)	59 (53, 68)	<0.01
EPP (mm Hg)	37 (29, 53)	57 (50, 75)	63 (56, 90)	<0.05
ZFP (mm Hg)	40 (33, 49)	19 (00, 29)	8 (-25, 20.7)	<0.05

adjusted by varying the height of the distal end to three different levels; these height levels exerted a downstream pressure of 41, 25 or 12 mm Hg. Thus a total of 24 sets of measurements were obtained. The FV in the insonated limb was measured using an 8 MHz probe at a fixed angle. PP was calculated from the formula PP=mean driving pressure – downstream pressure. Estimated PP (EPP) was calculated from the formula: EPP=(FV_{mean}/(FV_{mean}–$FV_{diastolic}$))×(mean driving pressure – diastolic driving pressure). The zero-flow pressure (ZFP) was calculated from the formula ZFP=mean driving pressure – EPP (Table 9).

Both PP and FV_{mean} increased significantly with the decrease in downstream pressure. Overall (n=24), mean EPP was higher than PP by 9.4 mm Hg (SD 19.9). However, the changes in PP were reflected by the changes in EPP and ZFP with 100% sensitivity. We conclude that moderate changes in PP can be assessed by the use of Doppler ultrasonography.

Keywords: measurement techniques, Doppler ultrasound; monitoring, pulse wave velocity; monitoring, zero-flow pressure

Reference

1 Belfort MA, Saade GR, Yared M, *et al. Am J Obstet Gynecol* 1999; **181**: 402–7

Non-invasive estimation of cerebral perfusion pressure and zero-flow pressure in healthy volunteers; effects of changes in carbon dioxide

S. M. Hancock*, R. P.Mahajan and L. Athanassiou*

University Department of Anaesthesia and Intensive Care, Queen's Medical Centre, Nottingham, UK

Zero-flow pressure (ZFP) in the cerebral circulation is the pressure at which blood flow ceases because of vessel closure.[1] [2] Recently a non-invasive method of estimating cerebral perfusion pressure (CPP) and ZFP has been described.[1] Carbon dioxide is a known modulator of cerebral vascular tone and therefore would be expected to affect CPP by altering arteriolar tone. We aimed to assess the effects of moderate changes in the end-tidal carbon dioxide partial pressure (PE'_{CO_2}) on the estimated CPP (ECPP) and ZFP using the recently described method.

We studied 17 healthy volunteers. Subjects lay supine and middle cerebral artery blood flow velocity (FV) was measured using a 2 MHz transcranial Doppler probe. Arterial pressure (AP, Finapres) and PE'_{CO_2} (using a facemask) were also measured. After the baseline measurements (breathing air), subjects were asked to hyperventilate to reduce their PE'_{CO_2} by approximately 1 kPa and measurements repeated. Volunteers were then asked to breathe through a Bain circuit and the fresh gas flow was adjusted to raise the PE'_{CO_2} by approximately 1 kPa. Measurements were repeated again after establishing a steady state.

The values for mean and diastolic FV and AP were used to calculate ECPP and ZFP using the following formulae:

$$ECCP=[FV_{mean}/(FV_{mean}-FV_{diastolic})]\times[AP_{mean}-AP_{diastolic}]$$

$$ZFP=AP_{mean}-ECPP$$

Changes in PE'_{CO_2} produced predictable significant changes in FV_{mean}. ECPP changed significantly during the study; it decreased with decreases in PE'_{CO_2} and vice versa. Accordingly, ZFP increased with decreases in PE'_{CO_2} and vice versa. Our results (Table 10) support the recent suggestion[2] that vascular tone is a major determinant of CPP and ZFP in the cerebral circulation.

Keywords: measurement techniques, Doppler ultrasound, transcranial; monitoring, cerebral perfusion pressure

Table 10 Mean (SD) values of end-tidal carbon dioxide partial pressure (PE'_{CO_2}), arterial pressure (AP), flow velocity (FV), estimated cerebral perfusion pressure (ECPP) and zero-flow pressure (ZFP)

	Hypocapnia	Baseline	Hypercapnia	*P* (ANOVA)
PE'_{CO_2} kPa	3.69 (0.34)	4.98 (0.31)	6.14 (0.38)	<0.001
AP_{mean} mm Hg	76.7 (12.43)	79.6 (9.35)	83.18 (10.98)	0.24
FV_{mean} mm Hg	31.71 (8.16)	46.29 (10.47)	58.53 (13.27)	<0.001
ECPP mm Hg	40.8 (9.28)	50.67 (8.33)	60.87 (9.28)	<0.001
ZFP mm Hg	35.9 (13.9)	28.9 (12.7)	22.3 (13.39)	0.017

References

1 Belfort MA, Saade GR, Yared M, *et al. Am J Obstet Gynecol* 1999; **181**: 402–7

2 Weyland A, Buhre W, Grund S, *et al. J Neurosurg Anesthesiol* 2000; **12**: 210–6

Accuracy of the Paedfusor—a new propofol target-controlled infusion system for children

D. Amutike*, A. Lal*, A. Absalom and G. N. C. Kenny

University Department of Anaesthesia, Glasgow Royal Infirmary and HCI Hospital, UK

Target-controlled infusion (TCI) systems are commonly used in adults but seldom in children. A prototype paediatric TCI system, the Paedfusor, has been developed. This system is similar to the commercially available adult system (Diprifusor), but uses a set of pharmacokinetic parameters and algorithms specific for children. The constants are as follows: k12=0.114, k13=0.0419, k21=0.055, k31=0.0033. Central compartment volume and k10 vary with age and weight. For children 12 yr and younger they are as follows: V1=458.4 ml kg^{-1}, k10=0.1527 × (weight ^–0.3). For children older than 12, these values are adjusted on a sliding scale between the values for younger children, and those used in the 'Diprifusor'.[1] The aim of our study was to assess the predictive performance of the Paedfusor.

Twenty-nine children undergoing cardiac catheterization or cardiac surgery were recruited into the study. Anaesthesia was induced and maintained using the Paedfusor system. Arterial blood samples (0.5 ml) were obtained at the following times: 3 and 8 min after induction; 60–90 s after a decrease of the propofol target; during stable anaesthesia; during cardiopulmonary bypass; on stopping the TCI pump; 3 and 8 min after stopping the TCI pump; and on eye opening. Samples were stored and were later assayed for whole blood propofol concentration (C_m). The predicted propofol concentration (C_{pred}) was recorded every time a blood sample was collected. For each sampling point, prediction error (PE) was calculated from the equation:

$$PE\ (\%)=((C_m-C_{pred})/C_{pred})\times 100$$

The PE was then used to calculate the median prediction error (MDPE), median absolute prediction error (MDAPE) and wobble.

Table 11 Performance of the Paedifusor

	MDPE (%)	MDAPE (%)	Wobble (%)
Non-bypass patients (n=8)	5.5	12.6	9.1
Bypass patients (n=21)			
Before bypass	3.1	7.9	6.9
During bypass	–5.5	7.6	5.2
After bypass	7.9	17.5	14.1
All patients	4.1	9.7	8.3

MDPE and MDAPE are measures of bias and precision, respectively.

The mean (range) age of the patients was 6.85 (1–15) yr and the mean (range) weight 21.18 (5–53) kg. MDPE, MDAPE and wobble for the Paedifusor are shown in Table 11.

The values for bias and precision of the Paedfusor compare very favourably with the results obtained in a study using modified paediatric microconstants[1] which showed a bias of 2.8% and precision of 16.2%. The Paedfusor performance indices, MDPE and MDAPE, were much better than those found in adult patients using the Diprifusor (MDPE of 16% and MDAPE of 24%).[2]

Keywords: anaesthetic techniques, intravenous; anaesthesia, paediatric

References

1 Marsh B, White M, Morton N, Kenny GN. *Br J Anaesth* 1991; **67**: 41–8
2 Swinhoe CF, Peacock JE, Glen JB, Reilly CS. *Anaesthesia* 1998; **53** (Suppl 1): 61–7

POSTER PRESENTATIONS

Comparison of external jugular and central venous pressures in mechanically ventilated patients on the intensive care unit

J. L. Parker*, B. Agarwal*, W. Russell*, C. Flucker and J. P. Thompson

University Department of Anaesthesia, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

Central venous pressure (CVP) monitoring is commonly used in intensive care but catheter insertion is not without complications.[1] The external jugular vein (EJV) can be cannulated simply and external jugular venous pressure (EJVP) has been shown to agree closely with CVP in anaesthetized, mechanically ventilated patients.[2] Our aim was to compare EJVP with conventional CVP measurement in clinical practice on the intensive care unit.

Twenty patients requiring mechanical ventilation on the intensive care unit with a central venous catheter *in situ* were recruited. A 20G 32 mm cannula (Abbocath, Abbot) was inserted into the EJV. The distal lumen of the CVP catheter and the external jugular cannula were connected to the same transducer via a three-way tap. Seven sets of paired measurements of mean venous pressure were taken at 60 min intervals by a blinded observer, at end-expiration and in random order. No changes in fluid therapy, inotropes, ventilation or posture were made during measurements.

One hundred and thirty-nine paired measurements were analysed from 20 patients (Figure 6). Median (range) CVP and EJVP were 11.2 (1–21) and 11.7 (1–23) mm Hg, respectively. The mean (SD) difference between CVP and EJVP was –0.5 (2.0) mm Hg, with limits of agreement of –4.4 to +3.4 mm Hg (95% confidence interval –4.7 to +3.7 mm Hg).

Previous studies using femoral venous catheters have accepted limits of agreement of approximately 2 mm Hg.[3] [4] Our results suggest that EJVP is a somewhat less accurate estimate of CVP in patients on the intensive care unit. This will limit the clinical use of this technique.

Keywords: monitoring, central venous pressure; veins, jugular

References

1 Agee KR, Balk RA. *Crit Care Clin* 1992; **8**: 677–86
2 Parker JL, Flucker C, Maguire A, Russell W, Thompson JP. *Br J Anaesth* 2000; **85**: 165P
3 Joynt GM, Gomersall CD, Buckley TA, *et al. Lancet* 1996; **347**: 1155–7
4 Kwok HM, Joynt GM, Tan P. *Crit Care Med* 1998; **26**: 461–4

Written consent for anaesthesia: anaesthetists' and patients' views

A. H. Bilolikar* and C. M. Timberlake*

King's College Hospital, Denmark Hill, London SE5 9RS, UK

Written anaesthetic consent is a contentious issue. The Department of Health recommends it,[1] while a working party of the Association of Anaesthetists of Great Britain and Ireland 'does not believe that it is necessary to have anaesthetic consent forms signed by patients'.[2] A postal survey was performed to determine current practice among anaesthetists and their views on the need, purpose and content of written consent. A simultaneous separate survey of the general public was conducted to ascertain their views on consent for anaesthesia and the information they would like to receive from their anaesthetist.

A questionnaire was posted to 264 anaesthetic college tutors in Great Britain. A reply-paid envelope was included to improve the response rate. In addition, the receptionist in our day surgery unit randomly assigned questionnaires to patients and their companions awaiting anaesthetic pre-assessment.

One hundred and sixty-one (61%) of the college tutors replied. The majority (83%) said they were not currently obtaining written anaesthetic consent, while 8% always did so and 9% sometimes

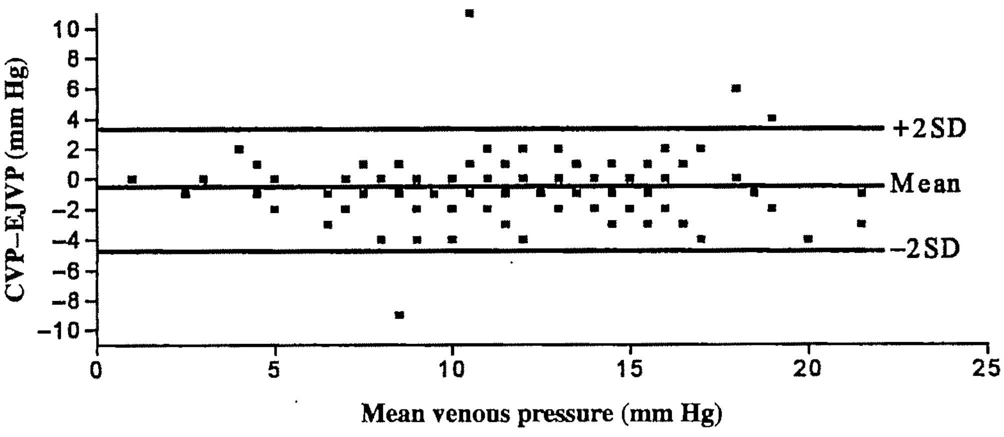

Fig 6 Bland–Altman plot comparing CVP with EJVP.

did. Only 18% felt that written consent was necessary, 70% considering it unnecessary and 17% being unsure. Legal protection was the most commonly cited reason (56% of responders) for obtaining written consent, while fewer (43%) considered it a useful way to ensure the patient is fully informed about anaesthesia. Forty-eight per cent thought that the risk of death or major disability should be explained to all patients when obtaining consent while 78% felt it appropriate that only minor complications should be discussed. A clear trend to obtain written consent from only high anaesthetic risk groups (62/91) was apparent. Conversely, only 12/72 would like to obtain written consent from low-risk groups.

Of the 197 lay people who completed questionnaires, 147 (75%) had previously had a general anaesthetic. Forty-nine per cent of this sample said they would like to know about a quoted one in 200 000 risk of death from anaesthesia in a healthy person, with 43% not wishing to know. Seventy-two per cent, however, said they wanted to be told about minor complications. Forty-nine per cent did want to sign an anaesthetic consent form, which was separate from the surgical consent, 39% did not and 11% were unsure. There appeared to be no significant difference in these views when comparing older and younger people.

The majority of anaesthetists surveyed remain to be convinced about the need for written anaesthetic consent. It appeared that medicolegal reasons would be the major driving force to change practice. The lay public had a different view, however, with almost half considering written consent to be appropriate. Our survey population wanted to be informed about all risk, with almost half wishing to know about a possible one in 200 000 risk of death.

Keywords: anaesthesia, written consent

References

1 *A Guide to Consent for Examination and Treatment.* London: Department of Health; 1990

2 *Information and Consent for Anaesthesia.* London: Association of Anaesthetists of Great Britain and Ireland; 1999

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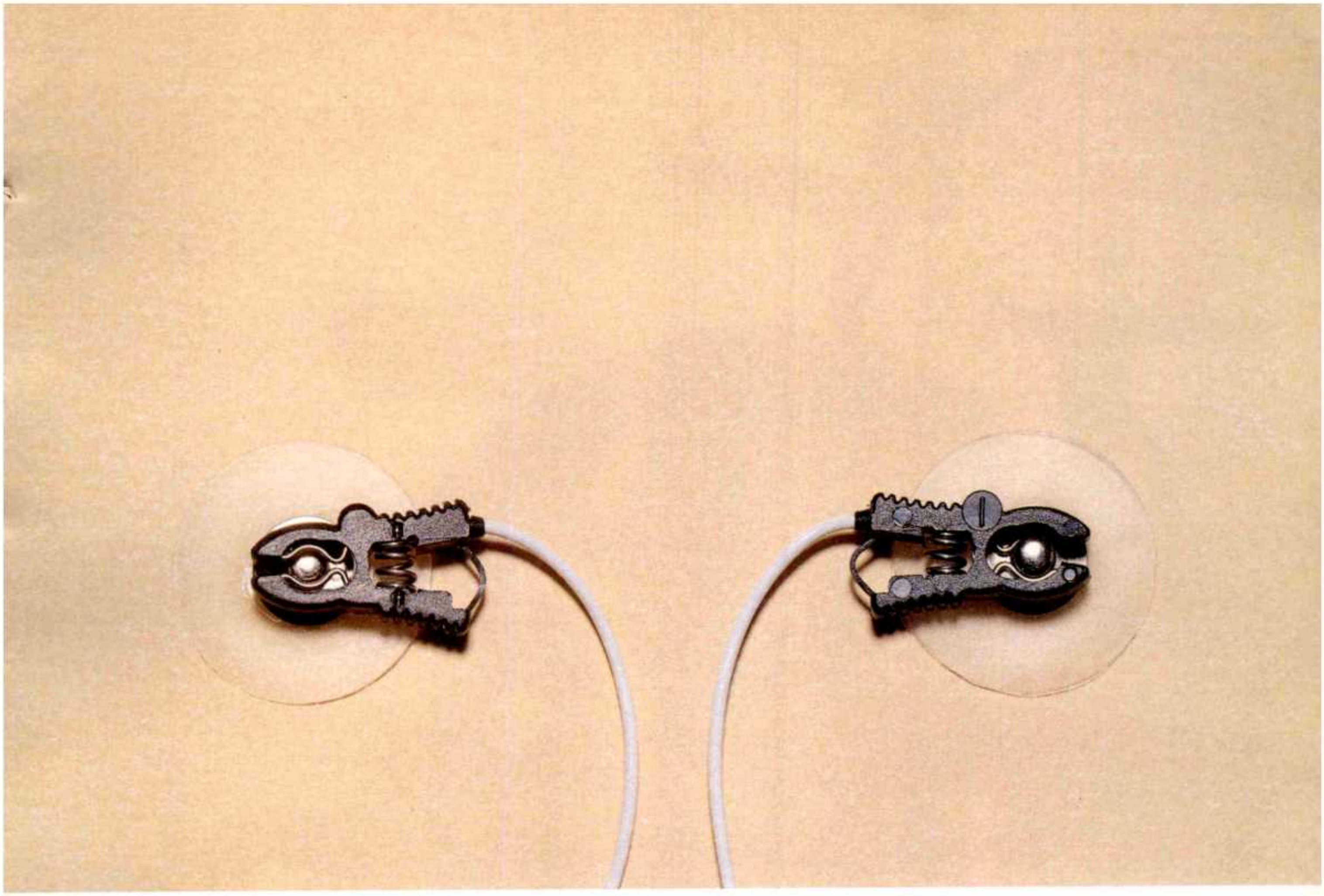

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hypertension. Maintain appropriate supervision when treating
elderly or patients with renal, hepatic or cardiac dysfunction
rofecoxib. In clinical studies, some osteoarthritis (OA) patients tre
with rofecoxib developed perforations, ulcers or bleeds (PU
Patients with a prior history of a PUB and patients greater th
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The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.

[Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very rare (<1/10,000) and isolated cases]

Body as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *Uncommon:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, including angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity inclu hepatic failure and jaundice.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58. Oral Suspen 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers:

Tablet 12.5 mg: PL 0025/0383; Tablet 25 mg: PL 0025/0 Oral Suspension 12.5 mg/5 ml: PL 0025/0385; Oral Suspen 25 mg/5 ml: PL 0025/0386.

Marketing Authorisation holder: Merck Sharp & Dohme Lim Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** February 2001

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References:

1. Bombardier C, Laine L, Reicin A et al. Comparison of u gastro-intestinal toxicity of rofecoxib and naproxen in patients rheumatoid arthritis. *N Engl J Med* 2000;343(21):1520-1528.

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Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

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References:

1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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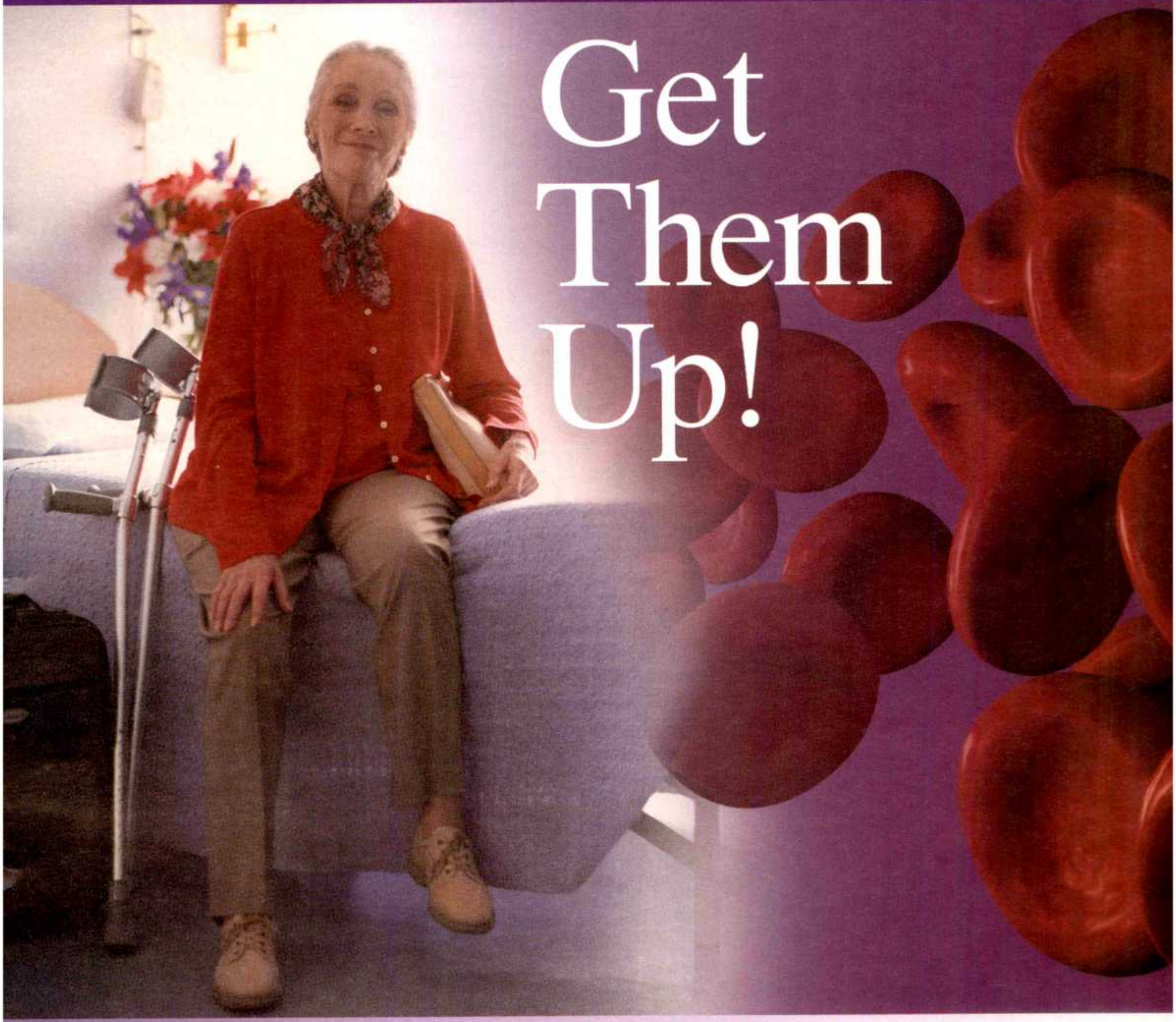

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Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* from 1 May, 2001 should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

Edinburgh Anaesthesia Festival

Edinburgh, UK, August 22–24, 2001

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2001 Edinburgh International Festival of the Arts.

The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information please contact: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: +44 (0) 131 536 3652; Fax: +44 (0) 131 536 3672; E-mail: anaes@ed.ac.uk

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Ventilation Through the Ages

ERMEC, Hull Royal Infirmary, Hull, UK, September 10–12, 2001

International ventilation conference covering all aspects of respiratory support from neonates through to adulthood.

To be placed on the list for registration details, please contact: Sue Hubbard, ERMEC, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK. Tel +44 (0)1482 674007; Fax: +44 (0)1482 586587; E-mail: suehermec@hotmail.com

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)

Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Depart-

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ment of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 2604472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Final FRCA Revision Course

Leicester, UK, October 2–5, 2001

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice will be held at Leicester Royal Infirmary. Fees: £290 non-residential (including lunch and refreshments); £390 residential (including lunch and refreshments). Course director is Dr Jonathan Thompson. Places are strictly limited. Please telephone Christine Gethins on +44 (0) 116 258 5291 (anae@le.ac.uk) for a booking form.

Dingle 2001—3rd Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 3–7, 2001

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

4th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 8–11, 2001

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. New! Core Topics for your Personal Portfolio. Guest Speakers, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1, 2001. Meeting approved for CEPD.

For full information and to secure a place, please visit: www.anaesthesiaupdates.com or contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk

Annual Meeting of the International Society for Anaesthetic Pharmacology (ISAP) (formerly SIVA)

New Orleans, Louisiana, October 12, 2001

For further information contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: larshq@iars.org; Web address: www.isaponline.org

The Royal College of Anaesthetists Senior Fellows Club Inaugural Meeting

Royal College of Anaesthetists, Thursday, October 24, 2001 (11.30–14.00)

Speaker: Dr John Nunn 'Climate change and extinction'

This meeting is open to anyone retired from full-time anaesthetic practice who has been associated with the college. The president will give a brief summary of current collegiate activities. Cost £15 to cover buffet lunch and drinks. Places are limited.

Apply to Mrs Mandie Kelly, The Royal College of Anaesthetists, 48/49 Russell Square, London WC1B 4JY, UK.

Tel: +44 (0)20 7813 1900. Fax: +44 (0)20 7813 1876. E-mail: mkelly@rcoa.ac.uk

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

5th Annual Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists

Bangalore, India, November 2–4, 2001

It is hoped that there will be a CMF in cardiac anaesthesia on one day preceding the conference, for the benefit of the postgraduate students.

For further information, please contact: Dr Suresh K. Ghaste, Organising Secretary, VIACTA Conference, Professor and Head of Department of Anaesthesiology, Sri Jayadeva Institute of Cardiology, M. H. Complex, Bangalore, S60 002, India. Tel: + 0 6707575 Ex. 138, E-mail: skghaste@yahoo.com

European One Day Course in Spinal Endoscopy

Bradford Royal Infirmary, England, November 9, 2001

This course will be of interest to all those involved with central neural blocks and especially to those involved with the investigation and management of patients with back and radicular pain.

For further information and to secure a place please contact: Dr J. Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford BD9 6RJ, England. Tel: +44 (0) 1274 364271; Fax: +44 (0) 1274 366811

International Scientific Meeting to celebrate the retirement of Professor R. S. Jones OBE, after 40 years in Veterinary Anaesthesia

The Racecourse, Chester, UK, December 6–7, 2001

Theme for the first day: 'Forty Years of Veterinary Anaesthesia'.
Theme for the second day: 'One Vet's Multidisciplinary Contributions'.

For further details please contact: Professor J. M. Hunter. Tel: +44 (0)151 706 4008; Fax: +44 (0)151 706 5884; E-mail: jwa@liv.ac.uk

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC–2002)

Mumbal, India, January 12–13, 2002

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbal: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; E-mail: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: **(Deadline – November 1, 2001)** Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques. Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

For full information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox. co.uk; Website: www.anaesthesiaupdates.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510; E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Austrian International Congress 2001 and Rudolf Kucher Forum

Anaesthesia & Intensive Care: The Emerging Discipline
September 12–14, 2001 Vienna, Austria

The abstracts will be available online only to BJA subscribers in September 2001, see http://bja.oupjournals.org. Delegates will receive print copies at the meeting. Extra print copies may be ordered for despatch in September 2001 from the Journals Subscriptions Department (Tel. +44 (0)1865 267907, Fax. +44 (0)1865 267485, email: jnls.cust.serv@oup.co.uk), price £24/US$38.

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ANESTHESIA & ANALGESIA

*Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists,
the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia,
the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia.*

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BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 87, Number 2, August 2001

Editorial I

Nitric oxide as mediator, marker and modulator of microvascular damage in ARDS

In this issue, Stuart-Smith and Jeremy join an interesting series of international debates regarding mechanisms of microvessel damage in acute respiratory distress syndrome (ARDS), in particular the role of endothelium derived relaxing factors (EDRF) in the pathophysiology and treatment of this disease.[1] Their review seems to promote the idea of endothelium-derived hyperpolarizing factor playing a primary role in ARDS whereas nitric oxide (NO), a prominent endothelium derived relaxing factor and regulator of intercellular communication, is attributed only as a minor component. The major claim of the authors, as reflected in the title, is that NO may not be the answer to microvessel damage in ARDS. This claim should certainly be investigated in the context of specific questions and in the context of our success or failure in understanding this life-threatening condition.

Do we understand the biology of ARDS?

The main characteristics of ARDS is non-cardiogenic pulmonary oedema and a mild degree of hypertension that results from acute alveolar injury causing respiratory insufficiency, decreased compliance, tissue hypoxaemia and multi-organ failure.[2–4] Although the exact cellular and molecular basis for ARDS remains uncertain more than 30 years after the original description of the syndrome, an intense and dynamic inflammatory response as discussed in the review of Stuart-Smith and Jeremy has been implicated in the microvascular and alveolar damage. A considerable body of experimental work appears to suggest that endotoxin, enhanced leukocyte and endothelial activation, and interaction with upregulation of a pro-inflammatory cytokine network all culminating in extensive oxidative stress are important components of the pathology underlying ARDS.[5] Complementing the observational and descriptive studies identifying these mechanisms, there is enormous research showing the functional and survival benefit from sophisticated treatments that efficiently neutralize some of these components including anti-endotoxin molecules, neutralizing antibodies against pro-inflammatory cytokines, neutrophil adhesion molecules, and recombinant and engineered antioxidants in a wide range of animal studies.[6] These studies clearly demonstrate our ability to successfully prevent alveolar damage in controlled laboratory situations with one or more intelligent therapeutic strategies. As it is pointed out in many recent editorials and reviews on ARDS, none of these strategies, however, decreased mortality among patients with ARDS.[2 3]

This important discrepancy between the success in the animal studies and failure in the clinical situation can be explained by a number of variables. These include: the dynamic nature of the condition and the already established dysfunction at the time of admission and treatment; great heterogeneity of the patient population; and lack of biochemical predictors of endothelial and epithelial injury to identify patients who may benefit from a given treatment strategy.[3] Another, more pessimistic opinion could be that similarly to septic shock, the therapeutic premises in ARDS may be flawed.[7] Targeting endotoxin or inhibiting the host inflammatory response in humans may not be beneficial. Studies of pro-inflammatory cytokines have shown that no single cytokine consistently predicts either the onset or the outcome of ARDS.[8] In contrast, it is becoming increasingly recognized that immune cells operate in a very complex network and they play both pathogenic and protective roles. Similarly, it is becoming clear that the balance of proinflammatory and anti-inflammatory factors, oxidants and antioxidants, and cytotoxic and protective factors determine the net inflammatory response and dysfunction in the lungs. Rather than targeting one single mediator or cytokine or immune cells, current efforts are directed at increasing our scientific knowledge of the complex timing of mediator release and the net pro-inflammatory, pro-oxidant and cytotoxic imbalance during early ARDS.

Our inability to treat established cellular injury might be related to deeper problems in our understanding of the biology of disease. While no one can doubt the significant progress in medical science related to molecular biology and chemistry, several great thinkers of cell biology voiced a critical opinion regarding the lack of our understanding of the determinants of normal 'living state', which is likely related to the dynamic and intimate supramolecular organisation especially of the cellular interior and physico-chemical properties of cytosol. As part of his introduction to electronic biology, the Nobel Prized Szent-Gyorgyi

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suggested that there were major 'gaps' in our understanding of the electronic and perhaps magnetic properties of intracellular structural proteins which he believed were the critical elements of the normal living state.[9] Similarly, Ling argued that a total and lasting cure of deadly diseases requires a re-evaluation of the physical basis of life and living matter.[10] Finally, Bulkley has offered the 'Life-as-Physics' paradigm for consideration since 'Life-as-Chemistry' as a singular theory to understand life has not solved any of the really basic mysteries of life.[11] Regarding ARDS, a better understanding of the physical basis of human endothelial and epithelial cell biology and survival might be needed to provide secure foundations to combat cellular injury in the future.

While we are currently not successful in treating acute lung injury there are indications that some of our efforts are successful in preventing further injury and might promote healing after the original insult. Recent improvements in supporting care of ARDS patients including aggressive treatment of underlying conditions such as infections, judicious fluid management and haemodynamic support and early enteral nutrition appear to slightly reduce mortality in individual centres when compared to historical controls.[3] It has also become apparent that improper mechanical ventilation might promote further injury on an already damaged lung. The use of inappropriate ventilation pressures and tidal volumes causing alveolar overdistension or repeated collapse and reopening has been shown to produce not only barotrauma but also an inflammation related lung injury. One of the most significant progresses in this field is the recent report by the ARDS Network demonstrating a 22% decrease in mortality in a randomized multicentre trial by a protective low tidal volume ventilation strategy in 861 patients with acute lung injury.[2] These recent data provide a framework and study structure, where additional protective strategies could successfully be tested. It might suggest that minimizing further injury and promoting lung healing might be achievable, and could be an important aspect of our efforts.

From this introduction it is obvious that no single molecule has been identified as the likely successful target of a potential magic bullet of cure for ARDS. Thus NO is not the only mediator which does not provide the full answer, but the real question is whether or not NO is involved in the complicated events underlying lung injury. In this setting, pulmonary vascular reactivity is only one of the determinants of the problem, which involves in addition changes in permeability, endothelial and epithelial physiology, cell injury and survival. We believe that there are ample theoretical considerations, experimental evidence and clinical observations to suggest that NO remains an important mediator, marker and modulator of alveolar damage in ARDS.

Nitric oxide has unquestionably occupied a pivotal position in lung research during the last 15 years. With the masterful discovery of EDRF and its identification as NO, basic scientists and clinicians have embarked on an important journey to study the relevance of this molecule in the pulmonary circulation and airway in both health and disease. This early period was characterised by extreme enthusiasm; NO achieved a status of the 'molecule of the year' in 1992 by *Science* with the lead article announcing 'NO News Is Good News'. The recent atmosphere with headlines of 'Just say NO to inhaled nitric oxide for ARDS', and 'Is nitric oxide inhalation a "cosmetic" therapy in ARDS?', and the article of Stuart-Smith and Jeremy obviously reflect a changing climate and reduced enthusiasm regarding the role of NO as a therapeutic strategy in ARDS.[12 13] But before we investigate this problem let us look into the potential role of NO and especially endogenous NO in normal lung physiology and during injury.

NO as regulator of pulmonary function and mediator of lung injury

As in the systemic circulation, the primary function of NO in the pulmonary vasculature is vasodilation. Although this is more easily demonstrated with conduit vessels, NO also functions in small vessels and regulates pulmonary vascular resistance in both animals and in humans. All three isoforms of nitric oxide synthase (NOS), neuronal (nNOS, NOS I), inducible (iNOS, NOS II), and endothelial (eNOS, NOS III), are expressed in the lung. Studies utilizing NO synthase inhibitors and selective targeted deletions of eNOS show acute modulation of pulmonary vascular tone in response to hypoxia in isolated perfused lungs of the mouse.[14] In chronic situations right ventricular systolic pressure was elevated in eNOS- and iNOS-deficient mice. Similarly, in humans, infusion of NO synthase inhibitor caused an increase in PVR and changes in pressure flow relationships demonstrating that tonic release of NO is an important regulator of pulmonary vascular tone.[15] These data strongly imply that contrary to the suggestion by Stuart-Smith and Jeremy, NO is an important feature of lung microvessels and is not a restricted feature of large vessels. Thus pathological conditions characterized by increased pulmonary vascular resistance may indeed be explained by attenuation of NO bioactivity.

Although the constitutive expression profiles of NOS in airway epithelial cells appear to be more complicated, it is conceivable to deduce that NO also acts by modulating bronchial tone and counteracts airway hyper-reactivity in stimulated conditions. A result of the bronchodilator and vasodilator effect might be co-ordination of ventilation and perfusion to the same alveoli. In addition to regulation of vascular tone, endogenous NO has been implicated in modulating capillary permeability. Although there appears to be some species variability, there is enough evidence to conclude that under normal conditions endothelial NO acts to reduce capillary permeability and attenuation of NO release by NOS inhibitors appears to augment oedema formation in the lung.[16 17]

While we argue strongly that the above considerations establish a potential role for endogenous NO to regulate microvascular injury in terms of vascular tone, reactivity and permeability, we agree with Stuart-Smith and Jeremy that NO appears to be a double-edged sword in the setting of lung injury. This likely relates to important characteristics of NO as a redox active molecule with great reactivity towards other reactive species and to its important ability to modulate cellular signal transduction.

Depending on the experimental conditions NO might act either as antioxidant or an oxidizing species. Under normal conditions NO is involved in mediating biological responses and a subtle oxidative stress associated with normal cellular metabolism is involved only in elucidating some oxidant-dependent signal transduction. Upon excessive oxidative stress, cellular constituents including proteins, nucleic acid and lipids become targets of the oxidizing species underlying cell injury. Under these conditions NO might react with a near diffusion limited reaction with superoxide to form peroxynitrite to further augment oxidative stress.[18] Equally important however is the efficiency of NO to terminate lipid peroxide propagation and to act as antioxidant in this situation.[19] These reactions are greatly modulated by the concentrations of reactants and the composition of the micro-environment in which these reactions take place. Importantly both of these reactions consume NO with the consequence of decreased availability of NO to elicit its normal bioactivity to mediate cGMP accumulation and vasodilatation.

Taking these considerations into account it is not surprising to recognize that there are data suggesting increased NOS expression, increased NO concentrations, peroxynitrite formation and modulation of lung injury in various experimental models and in the human situation. These changes appear to vary greatly depending on the stimulus used. In sepsis and LPS models, overproduction of NO appears to dominate perhaps via iNOS induction. This overproduction of NO might actually contribute to oxidative damage and increased permeability through peroxynitrite formation.[16 20] In other models of primary oxidative insult such as activated neutrophils, and ischaemia-reperfusion models, NO might reduce oxidative stress, neutrophil adhesion, pulmonary transit time and cellular injury.[21]

In addition to modulation of oxidative stress and antioxidant status, NO has implications to pro-inflammatory cytokine balance and apoptotic mechanisms. Cytokine release and upregulation of inflammatory genes largely depend on intracellular activation of NF-κB-transcription factor. There are important studies to show that NO might stabilise IκB, the protein primarily responsible for controlling NF-κB-activation.[22] Thus NO might be important in regulating the intensity and duration of pro-inflammatory cytokine activation. Similarly, NO has been implicated in the inhibition of caspase mediated apoptosis and conferring anti-apoptotic characteristics.[23] This might be an important aspect of NO mediated cytoprotection. However, in both of these respects NO can act not only as a friend but a foe activating NF-κB and causing apoptosis at higher concentrations. In any instance, these arguments do not lessen but strengthen the claim regarding the primary importance of NO as a potential mediator and modulator of microvascular damage in ARDS.

NO as a marker of lung injury

If NO plays such an important role can it be used as a biochemical marker of onset and disease activity, and as a predictor of outcome? The above considerations suggest that ARDS is associated with a complicated picture of NOS expression, NO generation and NO consumption and that NO concentrations will be different accordingly to the dynamically changing cytokine environment, the nature of airway inflammation, neutrophil activation, production of reactive oxygen species, and acidity in the immediate environment of endothelial and epithelial cells. In addition there are important sampling and methodological considerations. The dynamic nature of the disease, and the spatial heterogeneity of the pathological lesions would require serial samples from affected regions. Although there are no methods to sample lung tissue repeatedly in patients with ARDS, alveolar and bronchial cells might be obtained by bronchoalveolar lavage (BAL) and brushings, which might provide information about dynamism of NOS expression and its correlation with inflammatory and cytotoxic activities. Due to its short half-life, only stable products of NO can be analysed as nitrite and nitrate in BAL and blood specimens; these, however, may not reflect tissue levels and consumption of NO. There is interesting data regarding peroxynitrite formation and nitration of BAL and plasma proteins in ARDS, which require further confirmation and analysis.[20 24 25]

In addition to these biochemical assays, there has been an exciting development and attempt to investigate intrapulmonary levels of NO at the bedside by using analysis of exhaled gases. Many properties of NO favour partition between the fluid and gas phase and many fascinating and difficult questions remain in this rapidly developing field, the important progress allows us to formulate an hypothesis regarding the link between NO concentrations in exhaled breath and NO consumption in ARDS.[26 27] Current data suggest that similarly to experimental conditions, NO consumption reactions dominate in ARDS, since exhaled NO levels are lower in both fully developed ARDS and lung injury during transplantation.[26 28]

NO as modulator of lung injury

What about replacement therapy using intravenous and inhaled NO donors? If NO is consumed in ARDS, is it not the logical therapy of choice? Before we answer this question we have to admit that NO administration has already provided medicine with great therapeutic tools to help patients. Nitroglycerin is routinely used as a vasodilator and anti-anginal agent. Similarly, inhaled NO, a very simple respiratory therapy has provided anaesthetists with a much-needed selective pulmonary vasodilator of unmatched value in managing acute right ventricular failure even in the absence of lung injury. The surprising qualities including vasodilatation in ventilated regions of the injured lung thereby improving shunt and arterial oxygenation prompted the use of inhaled NO in ARDS.[29]

As pointed out by Claude Lenfant in his introduction to the monograph of *NO and the Lung* by Zapol and Bloch, 'The story of NO is almost unique in the sense that the original discovery... precipitated an urge for clinical and therapeutic application that often bypassed the need for further work on the fundamentals'.[30] The discovery of peroxynitrite and the central regulatory role of NO in pulmonary oxidant reactions appear to be two of these fundamentals.[18] These reactions might offset the many theoretical and potential benefits of inhaled NO in ARDS. Further studies will clarify whether these benefits can be unmasked by targeting reactive oxygen species and augmenting the efficiency of inhaled NO by specific phosphodiesterase inhibitors. We do not believe that we have an answer yet.

N. Marczin[1,2]
D. Royston[2]
[1]*National Heart and Lung Institute and Department of Anaesthesia*
Imperial College of Science
Technology and Medicine
Heart Science Centre
[2]*Department of Anaesthetics*
Royal Brompton and Harefield NHS Trust
Harefield Hospital, UK

References

1 Stuart-Smith K, Jeremy JY. Microvessel damage in acute respiratory distress syndrome: the answer may not be NO. *Br J Anaesth* 2001; **87**: 272–9

2 Anonymous. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301–8

3 Wyncoll DL, Evans TW. Acute respiratory distress syndrome. *Lancet* 1999; **354**: 497–501

4 Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1334–49

5 Hasleton PS, Roberts TE. Adult respiratory distress syndrome – an update. *Histopathology* 1999; **34**: 285–94

6 Conner BD, Bernard GR. Acute respiratory distress syndrome. Potential pharmacologic interventions. *Clin Chest Med* 2000; **21**: 563–87

7 Natanson C, Hoffman WD, Suffredini AF, Eichacker PQ, Danner RL. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann Intern Med* 1994; **120**: 771–83

8 Martin TR. Lung cytokines and ARDS: Roger S. Mitchell Lecture. *Chest* 1999; **116**: 2S–8S

9 Szent-Gyorgyi A. Bioelectronics and cancer. *J Bioenerg* 1973; **4**: 533–62

10 Ling GN. A physical theory of the living state: application to water and solute distribution. *Scanning Microsc* 1988; **2**: 899–913

11 Bulkley DH. An electromagnetic theory of life—II: Testing. *Med Hypotheses* 1992; **38**: 305–10

12 Matthay MA, Pittet JF, Jayr C. Just say NO to inhaled nitric oxide for the acute respiratory distress syndrome. *Crit Care Med* 1998; **26**: 1–2

13 Payen DM. Is nitric oxide inhalation a "cosmetic" therapy in acute respiratory distress syndrome? *Am J Respir Crit Care Med* 1998; **157**: 1361–2

14 Fagan KA, Tyler RC, Sato K, Fouty BW, Morris KGJ, Huang PL, McMurtry IF, Rodman DM. Relative contributions of endothelial, inducible, and neuronal NOS to tone in the murine pulmonary circulation. *Am J Physiol* 1999; **277**: L472–8

15 Cremona G, Wood AM, Hall LW, Bower EA, Higenbottam T. Effect of inhibitors of nitric oxide release and action on vascular tone in isolated lungs of pig, sheep, dog and man. *J Physiol* 1994; **481** (Pt 1): 185–95

16 Bernareggi M, Mitchell JA, Barnes PJ, Belvisi MG. Dual action of nitric oxide on airway plasma leakage. *Am J Respir Crit Care Med* 1997; **155**: 869–74

17 Sprague RS, Stephenson AH, McMurdo L, Lonigro AJ. Nitric oxide opposes phorbol ester-induced increases in pulmonary microvascular permeability in dogs. *J Pharmacol Exp Ther* 1998; **284**: 443–8

18 Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. *Proc Natl Acad Sci USA* 1990; **87**: 1620–4

19 Rubbo H, Radi R, Trujillo M, *et al.* Nitric oxide regulation of superoxide and peroxynitrite-dependent lipid peroxidation. Formation of novel nitrogen-containing oxidized lipid derivatives. *J Biol Chem* 1994; **269**: 26066–75

20 Haddad IY, Pataki G, Hu P, Galliani C, Beckman JS, Matalon S. Quantitation of nitrotyrosine levels in lung sections of patients and animals with acute lung injury. *J Clin Invest* 1994; **94**: 2407–13

21 Sato Y, Walley KR, Klut ME, English D, D'yachkova Y, Hogg JC, van Eeden SF. Nitric oxide reduces the sequestration of polymorphonuclear leukocytes in lung by changing deformability and CD18 expression. *Am J Respir Crit Care Med* 1999; **159**: 1469–76

22 Peng HB, Libby P, Liao JK. Induction and stabilization of I kappa B alpha by nitric oxide mediates inhibition of NF-kappa B. *J Biol Chem* 1995; **270**: 14214–19

23 Dimmeler S, Haendeler J, Nehls M, Zeiher AM. Suppression of apoptosis by nitric oxide via inhibition of interleukin-1 beta-converting enzyme (ICE)-like and cysteine protease protein (CPP)-32-like proteases. *J Exp Med* 1997; **185**: 601–7

24 Lamb NJ, Quinlan GJ, Westerman ST, Gutteridge JM, Evans TW. Nitration of proteins in bronchoalveolar lavage fluid from patients with acute respiratory distress syndrome receiving inhaled nitric oxide. *Am J Respir Crit Care Med* 1999; **160**: 1031–4

25 Gole MD, Souza JM, Choi I, *et al.* Plasma proteins modified by tyrosine nitration in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2000; **278**: L961–7

26 Marczin N, Riedel B, Gal J, Polak J, Yacoub M. Exhaled nitric oxide during lung transplantation [letter]. *Lancet* 1997; **350**: 1681–2

27 Marczin N, Exhaled nitric oxide in acute lung injury: measurements and physiological implications. In: Matalon S and Sznajder JI, eds. *Etiology and Treatment of Acute Lung Injury*. EOS Press, in press

28 Brett SJ, Evans TW. Measurement of endogenous nitric oxide in the lungs of patients with the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; **157**: 993–7

29 Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991; **83**: 2038–47

Editorial II

Sedation and analgesia—which way is best?

Practices vary in many areas of patient care, but one with a large degree of variability is the use of drugs to make patients comfortable—sedation and analgesia. Sedation and analgesia are common practice, with over 90% of patients in intensive care units (ICUs) needing them,[1] and costing 0.8–1.2 billion dollars in 1997.[2] The drugs used are potentially dangerous. Not only do they act on the central nervous system to reduce pain and suffering, but they also have many other effects.[3] These effects are widespread and as yet poorly understood; an example is their effect on the immune system.[4–6] What is clear is that if used carelessly, these drugs are a cause of morbidity, mortality and increased costs.

In these days of evidenced-based medicine, what is surprising is the large differences that exist between clinicians in using these drugs, even those working in the same ICU. Some of these differences may result from the background of the clinician. For example, physicians may lack some of the skills in regional analgesia possessed by anaesthetists, resulting in a greater use of parenteral opioids. Other reasons for the differences may involve availability (perhaps related to cost) or personal preference or prejudice. In this edition of the Journal, a group from Brussels[7] describe a survey, using email, of sedative and analgesic practices that looks at differences in 16 countries across western Europe. This survey is interesting for two reasons: (i) the method by which it was done; and (ii) the large differences in international variation that were shown.

The use of e-mails to send a questionnaire is novel and makes a pleasant change from the four sheets of paper and the (sometimes) stamped addressed envelope often used for such an exercise. The e-mail addresses used by the authors were collected from various sources, including conferences, databases, etc. This does, however, mean that only those who routinely use e-mails were available to respond. Those not used to using e-mails are unlikely to give their e-mail addresses, even if they have one. Furthermore, the advent of free e-mail addresses has led to many people changing their e-mail addresses at regular intervals. In the Eastern Area Intensive Care Group in the UK, 15–20% of members change their e-mail address every 2 years (M. Blunt, personal communication). This may, in part, explain the rather low response rate (20%) seen in this survey.

A further reason for the low response rate may have been the questionnaire being treated as just another uninvited, unexpected e-mail ('spam') and so being deleted on receipt. With the ease and low cost of sending email questionnaires, this way of doing surveys is likely to become popular. The risk is that it may lead to a barrage of questionnaires about aspects of the way we treat patients. I have no doubt some will be valuable and others of less value; even the good ones may be deleted just because of the number that may arrive.

The paper showed intriguing, marked national variations in sedative and analgesic practice. There are many possible reasons for them. For example, sedation and analgesia have many components. Most of these, such as anxiety or perception of pain, have a very strong cultural overlay. Stoical Northern Europeans *may* respond to these stimuli differently from temperamentally different Southern Europeans. However, the 75% need for continuous intravenous sedation in patients needing mechanical ventilation in the UK compared with only 30% in Italy is difficult to explain on grounds of temperament alone. An alternative explanation is the availability and cost of drugs. Midazolam only became available in Italy in the last 3 years. Propofol usage would be expected to be high as a consequence. Similarly, sufentanil is not available in the UK while alfentanil is. The recent licensing of dexmedetomidine by the Food and Drug Administration in USA, but the delay of its licence by the European Licensing Authority, may result in some interesting differences in sedative and analgesic practice between the USA and Europe. The likely future licensing of remifentanil for use in the critically ill in Europe will accentuate these differences.

A further reason for the difference is cost. This has been recognized as an important feature of sedative and analgesic drugs. Recent presentations[8 9] at the European Society of Intensive Care Meeting in October 2000 recognized the impact of new drugs in reducing these costs. Until recently, propofol was an expensive drug. This high cost may have influenced some countries in their choice of sedative and analgesic agents. If this is so, what is surprising is the high usage of propofol in the UK, a country with a relatively low expenditure on health care in Europe; perhaps it is a reflection of the large proportion of anaesthetists practicising intensive care in the UK.

This study,[7] in common with many others and some clinicians, assumes that midazolam and propofol are different versions of the same drug. This is clearly not so. Propofol is extremely good at inducing sleep, while midazolam is better at producing anxiolysis and amnesia. Perhaps some of the differences shown in this study result from clinicians in some countries recognizing these differences while those in others do not.

One surprising feature is the low usage of lorazepam. According to the American Society of Critical Care Medicine Guidelines,[10] lorazepam is the drug of choice for long-term sedation. It is inexpensive, thought to have inactive metabolites and is effective. Why, then, is it not used? There is some concern about the toxicity of the solvent, propylene glycol, which may inadvertently be given in large amounts with the potential risk of serious toxicity.[11] However, this is an unlikely explanation. More likely is that the guidelines are just not being followed, a common feature in this area of critical care. Other guidelines have also been developed to help with sedation and analgesia. Bair and colleagues[12] have looked at how well clinicians followed agreed guidelines about sedation. While the initial choice of drugs was as recommened in guidelines in 60% of patients, only guidelines were followed throughout a patient's ICU stay for only 23% of patients. The reasons given for not following the protocol were patient variability, clinicians' preference for other drugs and the guideline learning curve of residents. Why clinicians do not follow guidelines is an area of worthy study, since the introduction of guidelines has been shown to reduce significantly the mortality, morbidity and costs in this area.[2 13–16]

One of the difficulties in applying guidelines about sedation and analgesia is their applicability to individual patients. Part of this difficulty is how the effects of these drugs are measured. As yet there is no magic black box that generates a number to say if the effects are adequate or not. Perhaps one day! The bispectral index (BIS) looks promising,[17] but it is too early in its development to say how useful it will be. In the meantime we have to rely on clinical scales and scores.[18–22] These rarely have precise endpoints, unlike the measurement of heart rate or blood pressure used when giving catecholamines, or blood glucose concentration to guide insulin dosage. There are some measures of outcome, for example the Brussels group[23] have shown a reduction in sedative needs when a score is introduced. It is surprising, therefore, that in some countries sedation scoring is so poorly used, with only one in five ICUs in Austria routinely using one.

Sedation and analgesia are complex subjects. Sedation and analgesia are universally practised in ICUs throughout the world but, surprisingly, we know little about them. This study adds yet more questions for investigators to answer. By trying to explain these differences, it is hoped that we will improve the comfort of our patients while reducing risks and costs.

G.R. Park
Addenbrooke's Hospital
Cambridgeshire CB2 2QQ, UK

References

1 Dasta JF, Fuhrman TM, McCandles C. Patterns of prescribing and administering drugs for agitation and pain in patients in a surgical intensive care unit. *Crit Care Med* 1994; **22**: 974–80
2 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New Engl J Med* 2000; **342**: 1471–7
3 Wilkins M, Park GR. The peripheral effects of opioids. In: Schulte am Esch J, Scholz J, Tonner PH, eds. *Molecular Pharmacology of Anaesthesia*. Lengerich: PABST Science Publishers, 2000; 172–90
4 Tubaro E, Borelli G, Croce C, Cavallo G, Santiangeli C. Effect of morphine on resistance to infection. *J Infect Dis* 1983; **148**: 656–66
5 Beilin B, Shavit Y, Hart J, *et al.* Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. *Anesth Analg* 1996; **82**: 492–7
6 Galley HF, DiMatteo MA, Webster NR. Immunomodulation by anaesthetic, sedative and analgesic agents: does it matter? *Intensive Care Med* 2000; **26**: 267–74
7 Soliman HM, Mélot M, Vincent J-L. Sedative and analgesic practice in the intensive care unit: the results of a European survey. *Br J Anaesth* 2001; **87**: 186–92
8 Quinton P, Fletcher N, Royston D, Farrimond J, Reidel B. Propofol sparing effect of remifentanil when added to propofol for sedation in the intensive care unit. *Intensive Care Med* 2000; **26** (Suppl 3), S304
9 Motsch J, Bauer M, Böttinger BW, Martin E, Bach A. Cost effectiveness of dexmedetomidine for sedation in postoperative patients. *Intensive Care Med* 2000; **26** (Suppl 3), S306
10 Shapiro BA, Warren J, Egol AB, *et al.* Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med* 1995; **23**: 1596–600
11 Seay RE, Graves PJ, Wilkin MK. Comment: possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; **31**: 647–8
12 Bair N, Bobek MB, Hoffman-Hogg L, Mion LC, Slomka J, Arroliga AC. Introduction of sedative, analgesic, and neuromuscular blocking agent guidelines in a medical intensive care unit: physician and nurse adherence. *Crit Care Med* 2000; **28**: 707–13
13 Brook AD, Ahrens TS, Schaiff R, *et al.* Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; **27**: 2609–15
14 Saich C, Manji M, Dyer I, Rosser D. Efect of introducing a sedation guideline on sedative costs per bed day. *Br J Anaesth* 1999; **82**: 792–3
15 Marx CM, Smith PG, Lowrie LH, *et al.* Optimal sedation of mechanically ventilated pediatric critical care patients. *Crit Care Med.* 1994; **22**: 163–70
16 Saggs P. Sedation scoring in a general ICU—comparative trial of two assessment tools in clinical practice. *Nurs Crit Care* 1998; **3**: 289–95
17 Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; **89**: 980–1002
18 Ramsay MAE, Savege TM, Simpson BJR, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *Br Med J* 1974; **ii**: 656–9
19 Chernik DA, Gillings D, Laine H, *et al.* Validity and reliability of

the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; **10**: 244–51

20 Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation–Agitation Scale for adult critically ill patients. *Crit Care Med* 1999; **27**: 1325–9

21 Devlin JW, Boleski G, Mlynarek M, *et al.* Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999; **27**: 1271–5

22 O'Sullivan G, Park GR. The assessment of sedation. *Clin Intensive Care* 1990; **1**: 116–22

23 Detriche O, Berre J, Massaut J, Vincent JL. The Brussels sedation scale: use of a simple clinical sedation scale can avoid excessive sedation in patients undergoing mechanical ventilation in the intensive care unit. *Br J Anaesth* 1999; **83**: 698–701

Editorial III

BJA Concise — a step too far

The *BJA Concise* was not conceived without prolonged discussions at the Board of the British Journal of Anaesthesia. The arguments in favour of moving from conception to delivery depended on simultaneous availability of the full *BJA* on the Internet. The advantages of the *BJA Concise* were believed to be: economy in usage and distribution of paper; financial savings to the journal by a reduction in printing and postage charges (which became available for funding the production of The Royal College of Anaesthetists' Bulletin and *BJA:CEPD Reviews*); and indeed encouragement to our readers to use and augment their familiarity with the electronic mode of communication. Unfortunately, however, this view has not been shared by a large number of our readers and it is evident that the *BJA Concise* has proved to be deeply unpopular. Many of the reasons put forward by our readers are that it is not possible to access full articles in the *BJA* on a journey or at odd times during the day, that the Internet is not convenient for a quick transient check of some contents, that it discourages readers from accessing full articles, and that it allows satisfaction with summaries only (which is particularly detrimental to trainees). What is abundantly clear, to our surprise, is that Internet access is not available readily to a large number of our readers and the view of the BJA Board was obviously coloured initially by the fact that being predominantly academic in constitution, members have easy and readily available Internet access in university institutions.

We do not believe that we have made an error in principle. However, in pushing RCA subscribers towards a situation in which access to the full journal was available only via the Internet, we have clearly progressed too rapidly. Nonetheless, there is no doubt that at some stage in the future there will be a progressive move away from full paper copy of medical journals to Internet version only. It was our belief that the *BJA Concise* would act as a transitional stage in this process. It is clear from our readers' response, however, that this step has been taken too soon. We must therefore admit this error and as our remit is to provide not only the best possible service to potential authors but also to satisfy the demands of our readers, we have taken the decision to discontinue the *BJA Concise* for the foreseeable future and revert back to the full paper copy of the journal. Thus from July 2001 onwards, RCA subscribers will receive the full version of the *BJA* together with the RCA Bulletin and *BJA:CEPD Reviews*, and all subscribers will continue to obtain free Internet access to the full *BJA*. We apologize to our readers who have found the *BJA* unsatisfactory for volume 86, but I have no doubt that at some indefinable stage in the future the arguments in favour of a concise version of the *BJA* will be resurrected.

Graham Smith
Chairman of the Board
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CLINICAL INVESTIGATIONS

Sedative and analgesic practice in the intensive care unit: the results of a European survey[†]

H. M. Soliman, C. Mélot and J.-L. Vincent*

[1]*Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Route de Lennik 808, B-1070 Brussels, Belgium*

**Corresponding author*

Sedation and analgesia are important aspects of patient care on the intensive care unit (ICU), yet relatively little information is available on common sedative and analgesic practice. We sought to assess international differences in the prescription of sedative and analgesic drugs in western European ICUs by means of a short, self-administered questionnaire. Six hundred and forty-seven intensive care physicians from 16 western European countries replied to the questionnaire. Midazolam was used as a sedative often or always by 63% of respondents and propofol by 35%. There were considerable international variations, with midazolam being preferred over propofol in France, Germany, the Netherlands, Norway and Austria. For analgesia, the drugs most commonly used were morphine (33%), fentanyl (33%) and sufentanil (24%). Morphine was preferred over fentanyl and sufentanil in Norway, UK and Ireland, Sweden, Switzerland, the Netherlands, and Spain and Portugal. Fentanyl was preferred in France, Germany and Italy. Sufentanil was preferred in Belgium and Luxemburg and in Austria. Multivariate analysis showed that the combination of midazolam with fentanyl was most often used in France; propofol with morphine in Sweden, the UK and Ireland, and Switzerland; midazolam with morphine in Norway; and propofol with sufentanil in Belgium and Luxemburg, Germany and Italy. The use of a sedation scale varied from 72% in the UK and Ireland to 18% in Austria. When used, the most common sedation scale was the Ramsay scale. This study demonstrates substantial international differences in sedative and analgesic practices in western European ICUs.

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Anxiety and pain are commonly encountered by intensive care unit (ICU) patients, and almost all critically ill patients, particularly those receiving mechanical ventilation, will receive either a sedative or analgesic agent; many will receive both. A wide variety of pharmacological agents are now available for sedation and analgesia and, while recommendations have been made regarding the 'best' sedative and analgesic regimes for ICU patients,[1] practice varies widely between and within ICUs. The choice of agent can be based on many factors, including the relative needs for sedation and analgesia, the pharmacodynamics and pharmacokinetics of the drug in question, route and ease of administration, the tolerance profile and the cost. While many studies have been conducted comparing the effectiveness of various agents,[2–12] there is relatively little published information on variations in sedative and analgesic drug use among units or across national and international boundaries.[13–18]

The aim of our study was to assess differences in the clinical use of sedative and analgesic drugs, alone or in combination, in western European ICUs.

Methods

A short questionnaire was sent by e-mail to all names on a database, obtained from the European Society of Intensive Care Medicine, Intensive Care Symposium activities and other academic meetings, of ICU doctors in 17 western

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Table 1 Questionnaire used in study

NAME: .... **COUNTRY:** ....

1. In your ICU, what percentage of mechanically ventilated patients require continuous i.v. sedation?
   - ☐ <50%
   - ☐ 50–75%
   - ☐ 75–90%
   - ☐ 100%

2. In patients requiring a continuous infusion of sedative agents, how often do you use the following agents?

midazolam:	☐ never	☐ seldom	☐ regularly	☐ often	☐ always
propofol:	☐ never	☐ seldom	☐ regularly	☐ often	☐ always
other (please specify):	☐ never	☐ seldom	☐ regularly	☐ often	☐ always

3. What other intravenous sedative agents do you use regularly?

haloperidol:	☐ never	☐ seldom	☐ regularly	☐ often
other (please specify):	☐ never	☐ seldom	☐ regularly	☐ often

4. Do you use a sedation score? ☐ yes ☐ no
   If yes, what type?:
   - ☐ Ramsay score
   - ☐ locally developed score
   - ☐ SAS score
   - ☐ other

5. In patients requiring continuous infusion of analgesic agents, how often do you use the following agents?

morphine:	☐ never	☐ seldom	☐ regularly	☐ often	☐ always
fentanyl:	☐ never	☐ seldom	☐ regularly	☐ often	☐ always
sufentanil:	☐ never	☐ seldom	☐ regularly	☐ often	☐ always

6. Type of ICU (several answers possible)
   - ☐ medical
   - ☐ surgical
   - ☐ trauma
   - ☐ coronary
   - ☐ paediatric
   - ☐ burns

7. Type of hospital (one answer)
   - ☐ university/academic
   - ☐ city
   - ☐ community

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European countries: Belgium, Luxemburg, France, Germany, Netherlands, UK, Ireland, Finland, Denmark, Switzerland, Spain, Portugal, Greece, Italy, Austria, Sweden and Norway. The short questionnaire (Table 1) asked seven questions about the clinical use of sedative and analgesic drugs in ICU patients. Of the 3639 e-mail addresses, 340 were found to be incorrect and the messages were returned.

The answers were collected on a computer database. Univariate statistical analysis consisted of χ^2 tests or Fisher's exact tests. Multivariate statistical analysis was also performed, using multiple correspondence analysis. The level of statistical significance was set at $P<0.05$.

Results

We received 647 replies to the questionnaire (20% response rate) from 16 countries. For analysis, we pooled the answers from Luxemburg with those from Belgium, Portugal with Spain, and Ireland with the UK, because of the small number of responses (Table 2). Of the respondents, 49%, 35% and 16% were working in university, city and community hospitals, respectively.

Table 2 Response rates according to country

Country	Sent	Responses received (%)
Austria	180	40 (22.2)
Belgium	528	67 (12.6)
Denmark	134	23 (17.1)
Finland	75	15 (20)
France	632	175 (27.6)
Germany	371	76 (20.4)
Greece	73	0
Ireland	19	2 (10.5)
Italy	215	44 (20.4)
Luxemburg	7	2 (28.5)
The Netherlands	203	23 (11.3)
Norway	137	33 (24)
Portugal	127	5 (3.9)
Spain	141	12 (8.5)
Sweden	136	38 (27.9)
Switzerland	117	24 (20.5)
UK	524	68 (12.9)

The use of sedation in ventilated patients varied considerably between countries; 78% of respondents from the UK

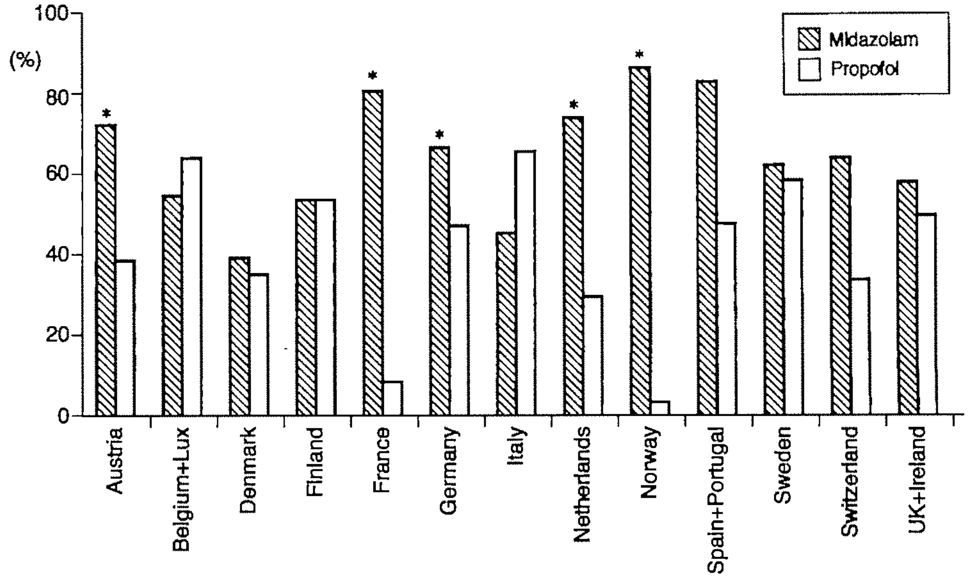

Fig 1 Prevalence of frequent use of midazolam and propofol (often or always) for sedation according to country. *$P<0.05$ between drugs for that country.

Table 3 Prevalence of frequent use (often or always) of sedative and analgesic drugs. *Used regularly or often.

Sedative drug	Number (%)	Analgesic drug	Number (%)
Midazolam	408 (63)	Morphine	214 (33)
Propofol	229 (35)	Fentanyl	214 (33)
Haloperidol*	58 (9)	Sufentanil	153 (24)
Clonidine	12 (1.8)	Piritramide	5 (0.7)
Ketamine	8 (1.2)	Others	7 (1)
Flunitrazepam	6 (0.9)		
Droperidol	5 (0.7)		
Alfentanil	5 (0.7)		
Lorazepam	3 (0.5)		
Diazepam	2 (0.3)		
Methohexital	2 (0.3)		

and Ireland stated that >75% of their ventilated patients required continuous intravenous sedation while in Italy the figure was just 30%.

Sixty-three per cent of respondents said they used midazolam often or always in patients requiring sedation, and 35% used propofol (Table 3). Although midazolam was the most commonly used sedative drug in both medical and surgical units, the common (often or always) use of propofol was more frequent in surgical units than in medical units (34% and 12%, respectively; $P<0.05$); the reverse was true for midazolam (55% and 88%, respectively; $P<0.05$). There was a highly significant difference ($P<0.01$) in the use of midazolam and propofol between countries. Midazolam was often or always used by 85% of respondents in Norway, but only by 39% in Denmark, and propofol was often or always used by 65% of Italian respondents, but only by 3% of respondents from Norway (Figure 1). Midazolam was more commonly used than propofol in France, Germany, the Netherlands, Norway and Austria ($P<0.05$), and propofol appeared to be more commonly used than midazolam in Italy, and Belgium and Luxemburg, although this was not significant (Figure 1). Lorazepam was used often or always by only three (0.5%) respondents.

Thirty-three per cent of respondents stated that they used morphine often or always in patients requiring continuous intravenous analgesia, 33% said they used fentanyl and 24% sufentanil (Table 3), with significant differences among countries. The common (often or always) use of morphine varied from 88% in Norway to 3% in Germany, that of fentanyl from 58% in Italy to 0% in the Netherlands, and that of sufentanil from 52% in Belgium and Luxemburg to 0% in Switzerland. Morphine was used more commonly than the other agents in the UK and Ireland, Sweden, Norway, Switzerland, Spain and Portugal, and the Netherlands ($P<0.05$). Fentanyl was preferred over the other agents in France, Germany and Italy ($P<0.05$), and sufentanil was preferred in Belgium and Luxemburg, and Austria ($P<0.05$) (Figure 2). There was no significant difference in the use of analgesic drugs between different types of ICU.

Multivariate analysis showed that the combination of midazolam and fentanyl was most often used in France, and that the combination of propofol and morphine was most used in Sweden, the UK and Ireland, and Switzerland. The combination of midazolam with morphine was most often used in Norway. The combination of propofol and sufentanil was most often used in Belgium and Luxemburg, Germany, and Italy (Figure 3).

The use of a sedation scale varied widely ($P<0.01$) around a mean of 43% (Figure 4), with doctors from the UK and Ireland most frequently using a sedation scale (72%), and those in Austria using one least often (18%). When a

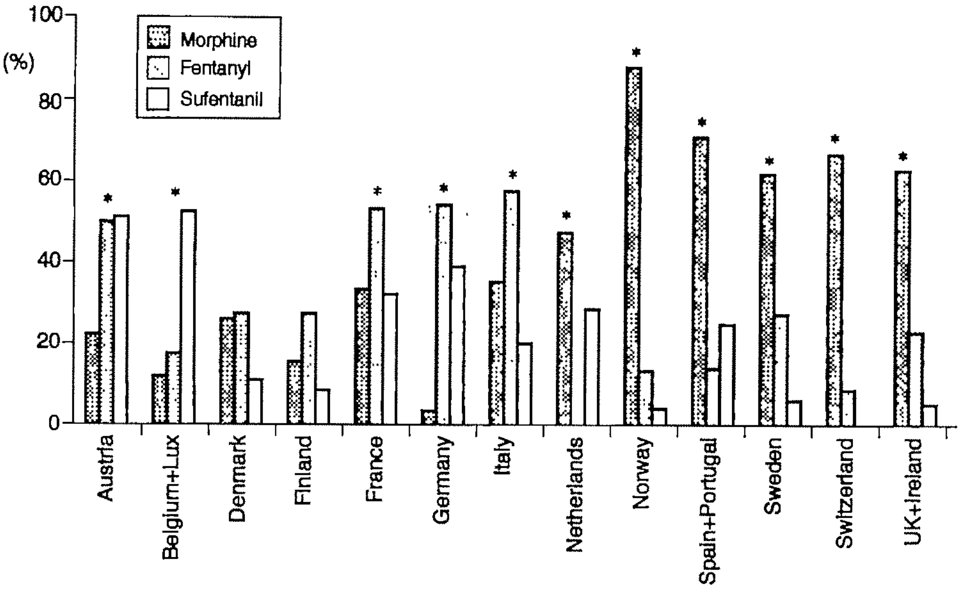

Fig 2 Prevalence of frequent use of morphine, fentanyl and sufentanil for analgesia according to country. $*P<0.05$ between drugs for that country.

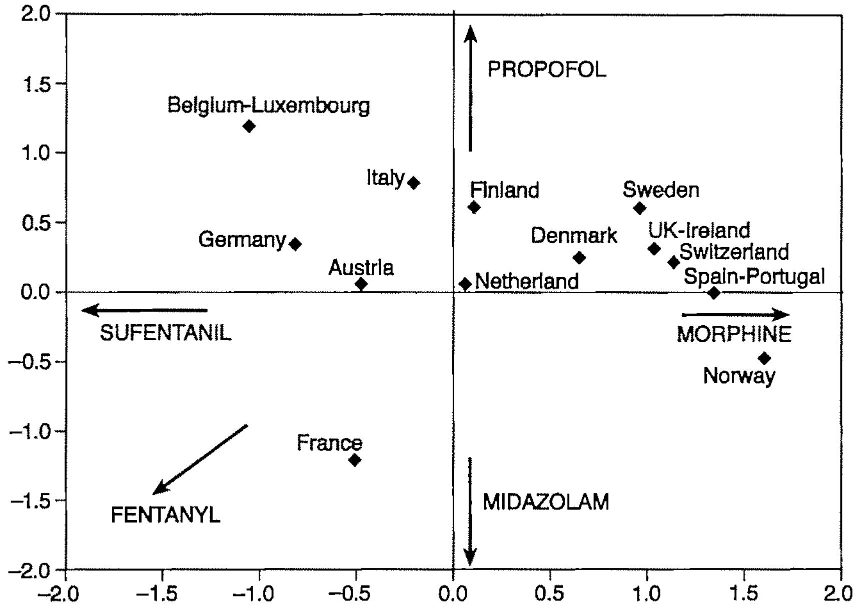

Fig 3 Sedative and analgesic drug combinations in different countries.

sedation scale was used, the Ramsay scale was employed most commonly (74% of cases).

Discussion

The ICU environment can appear hostile, even threatening, to patients; the noisy ICU environment, unfamiliar monitoring and support equipment, medical jargon, loss of day–night cycle and painful invasive procedures are associated with a high incidence of psychological problems and sleep deprivation.[19–21] Sedation and analgesia are important to ensure patient comfort, from both psychological and physical points of view. The stress response can lead to profound changes in endocrine function, hypermetabolism, sodium and water retention, mobilization of substrates from energy stores and increased lipolysis.[22 23] Pain can have many adverse consequences, including sympathetic overactivity with an increase in heart rate and myocardial oxygen consumption, increased respiratory rate and hypoxaemia, altered gastrointestinal motility, impaired urinary tract function, changes in blood viscosity, clotting time and

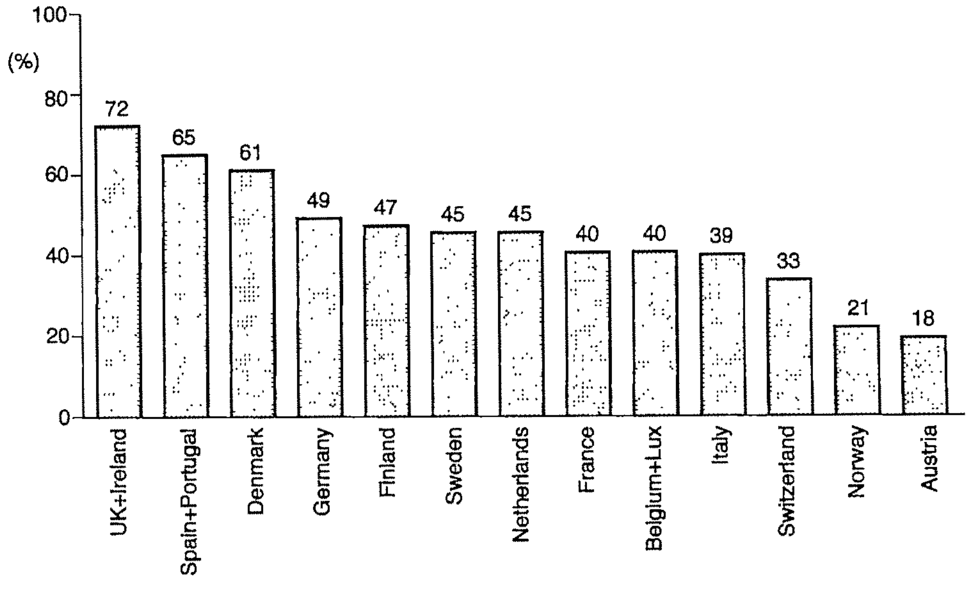

Fig 4 Prevalence of frequent use of sedation scale in each country.

platelet aggregation, diminished immune function and impaired wound healing.[24 25]

However, excessive sedation can have negative side-effects, including an increased risk of venous thrombosis, decreased intestinal motility, hypotension, reduced tissue oxygen extraction capabilities, prolonged ICU stay and increased costs.[26–30] An acute withdrawal syndrome following prolonged use of sedative or analgesic drugs has also been reported in ICU patients.[31] Ideally, administration of sedative and analgesic drugs should aim to keep the patient comfortable but easily aroused.[32] Attitudes may have changed over time, as suggested by two enquiries in the UK: in 1981, Merriman[33] reported that 67% of ICUs aimed to keep patients completely detached from the environment, whereas by 1987, Bion and Ledingham noted that 69% of respondents preferred patients sleepy but easily awakened.[14]

In 1995, the Society of Critical Care Medicine (SCCM) published practice parameters for intravenous analgesia and sedation in the ICU.[1] Evidence-based medicine recommendations regarding the 'preferred' agents were developed by a task force of more than 40 experts. Midazolam and propofol were preferred for short-term sedation, lorazepam for long-term sedation and haloperidol for treating delirium, while morphine and fentanyl were the preferred analgesic agents in critically ill patients.[1] Despite such guidelines, there are large differences in the use of sedative and analgesic agents among units and across national and international boundaries.[13–18 34] A survey of head nurses from 164 hospitals across the USA in 1991 found that 18 different sedative agents were used, with a preference for benzodiazepines and opiates.[15] Also in the USA, Dasta and colleagues[16] reported the use of 23 different agents for sedation and relief of anxiety and pain in their surgical ICU with extensive use of benzodiazepines (including, most commonly, lorazepam) and morphine. In our study, 22 different drugs were cited as being used often or always for sedation or analgesia, with midazolam, morphine and fentanyl generally being the preferred agents.

Benzodiazepines, e.g. diazepam, lorazepam and midazolam, are widely used as sedative agents in the ICU. Diazepam use has become less common as newer shorter-acting benzodiazepines have become available. Lorazepam is more potent than midazolam and, because of its low lipid solubility, crosses the blood–brain barrier more slowly, delaying its onset of action and prolonging the sedative effect.[6 35] Hence, it is recommended for longer-term sedation while midazolam is preferred for short-term sedation.[1] Propofol, another frequently used sedative agent, resembles midazolam in terms of pharmacological profile.[35] Studies comparing midazolam and propofol have generally shown the two agents to be of similar efficacy and safety in sedating various groups of critically ill patients.[4 5 9 36 37] Midazolam is, however, cheaper than propofol,[9 12 38 39] which may account for the preferred use of midazolam seen in our study and others.[17 18 40] Nevertheless, some would argue that propofol, when used as a sedative in mechanically ventilated patients, is associated with shorter weaning times and hence, while midazolam may be cheaper, the overall cost–benefit analysis taking into account duration of mechanical ventilation and ICU stay may in fact be better with propofol.[2 8]

We also found great differences in the drugs most commonly used for analgesia, although morphine and fentanyl were most commonly prescribed, a finding supported by other groups[15 16 18 34 40] and in accord with the recommendations of the SCCM.[1] Opioids, generally administered as a continuous intravenous infusion, remain the mainstay of ICU analgesia. Morphine is the most widely used of the opioids, possibly again related to its lower cost,[38] although the shorter-acting fentanyl and sufentanil are preferred by some.

Importantly, sedative and analgesic drugs are distinct agents, having separate, although complementary and sometimes synergistic, actions.[41 42] Combined use of these drugs is common in the ICU patient; Watling and colleagues[34] reported that 25% of patients received combination drug therapy, 46% of whom received a benzodiazepine–opiate combination. Magarey[17] reported that, in Australia, the most common form of sedation was a benzodiazepine–opiate combination (used in 88% of ICUs), notably morphine with midazolam. In our study, the particular combination of drugs differed among countries, with, for example, midazolam and fentanyl preferred in France, but midazolam and morphine preferred in Norway.

While it was not the aim of the questionnaire, it is interesting to speculate on the reasons behind the differences in sedative and analgesic use seen among western European countries. The costs of drug therapy are certainly important and international differences in drug price may exist as a result of individual pricing policies, costs of transport and packing, and the cost of the mark-up added to the price of drugs by the importer and distributor.[43] Several groups have reported lorazepam to be an effective sedative agent with lower costs than midazolam or propofol,[6 11 12] and yet lorazepam was used often or always by only three of our respondents.

Differences in the timing of drug registration in various countries may account for certain preferences. As an example, the fact that midazolam has only recently been registered in Italy may explain why propofol was used more than midazolam in Italy, while the fact that sufentanil is less easily available in the UK may explain why morphine and fentanyl were used more than sufentanil in the UK. The primary speciality of the intensivist questioned may also influence drug choice; for example, anaesthetists may favour anaesthetic agents more than intensivists with a general medical background. While the design of our questionnaire did not allow us to investigate this aspect specifically, it is interesting to note that propofol was used more frequently on surgical than on medical units, perhaps related to its common use as an anaesthetic agent. It may also be preferred to facilitate earlier weaning and extubation.[3 12] Communication with patients by verbal and non-verbal methods, such as touch by staff or relatives, is very important and depends on individual cultural, educational and socio-economic differences.[44] This may decrease the need for sedation, although it may not significantly affect the choice of agent.

Both under- and over-sedation can have negative effects on the ICU patient,[10] and in this population, particularly those who are mechanically ventilated, the level of sedation is often difficult to assess. Various sedation scales and scores have been developed in order to facilitate this process,[45–50] and the use of a sedation scale has been shown to reduce the numbers of patients with excessive degrees of sedation.[50] However, many units still rely on staff assessment of sedation rather than routinely employing any of the available scoring systems. Watling and colleagues[34] reported that just 26% of the respondents in their survey of ICUs in the USA used a sedation scale, while Christensen and Thunedborg[18] noted that only 16% of Danish ICUs used a sedation scoring system. In our study, we found that 43% of units used a scale, but this figure varied greatly among individual countries. As we report, the Ramsay scale[45] is generally the most widely used sedation assessment system, probably chiefly because it is easy to apply, although it has never been scientifically tested for reliability or validity.[51]

In conclusion, our enquiry has revealed substantial international differences in the clinical use of drugs for sedation and analgesia in western European countries, and in the use of sedation scales to monitor levels of sedation. While we acknowledge the inherent limitations of questionnaire surveys and accept that the response rate was relatively low, we received replies from a broad cross-section of ICUs and hospital types, and have no reason to believe the data obtained are not representative of the current situation in western Europe. Such information can encourage valuable discussion about the reasons behind the variations seen, and perhaps help in the development of sedation and analgesic protocols, which have been shown to improve outcome.[52]

References

1 Shapiro BA, Warren J, Egol AB, *et al.* Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; **23**: 1596–600

2 Carrasco G, Molina R, Costa J, Soler JM, Cabre L. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost–benefit analysis. *Chest* 1993; **103**: 557–64

3 Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR. Comparison of the sedative and amnesic effects of midazolam and propofol. *Br J Anaesth* 1993; **70**: 612–6

4 Ronan KP, Gallagher TJ, George B, Hamby B. Comparison of propofol and midazolam for sedation in intensive care unit patients. *Crit Care Med* 1995; **23**: 286–93

5 Kress JP, O'Connor MF, Pohlman AS, *et al.* Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. *Am J Respir Crit Care Med* 1996; **153**: 1012–18

6 Cernaianu AC, DelRossi AJ, Flum DR, *et al.* Lorazepam and midazolam in the intensive care unit: a randomized, prospective, multicenter study of hemodynamics, oxygen transport, efficacy, and cost. *Crit Care Med* 1996; **24**: 222–8

7 Chamorro C, de Latorre FJ, Montero A, *et al.* Comparative study of propofol versus midazolam in the sedation of critically ill patients: results of a prospective, randomized, multicenter trial. *Crit Care Med* 1996; **24**: 932–9

8 Barrientos-Vega R, Mar S, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. *Crit Care Med* 1997; **25**: 33–40

9 Weinbroum AA, Halpern P, Rudick V, Sorkine P, Freedman M, Geller E. Midazolam versus propofol for long-term sedation in the ICU: a randomized prospective comparison. *Intensive Care Med* 1997; **23**: 1258–63

10 Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med* 1998; **26**: 947–56

11 Swart EL, van Schijndel RJ, van Loenen AC, Thijs LG. Continuous infusion of lorazepam versus midazolam in patients in the intensive care unit: sedation with lorazepam is easier to manage and is more cost-effective. *Crit Care Med* 1999; **27**: 1461–5

12 McCollam JS, O'Neil MG, Norcross ED, Byrne TK, Reeves ST. Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison. *Crit Care Med* 1999; **27**: 2454–8

13 Merriman HM. The techniques used to sedate ventilated patients. A survey of methods used in 34 ICUs in Great Britain. *Intensive Care Med* 1981; **7**: 217–24

14 Bion JF, Ledingham IM. Sedation in intensive care—a postal survey. *Intensive Care Med* 1987; **13**: 215–16

15 Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. *J Am Med Assoc* 1991; **266**: 2870–75

16 Dasta JF, Fuhrman TM, McCandles C. Patterns of prescribing and administering drugs for agitation and pain in patients in a surgical intensive care unit. *Crit Care Med* 1994; **22**: 974–80

17 Magarey JM. Sedation of adult critically ill ventilated patients in intensive care units: a national survey. *Aust Crit Care* 1997; **10**: 90–93

18 Christensen BV, Thunedborg LP. Use of sedatives, analgesics and neuromuscular blocking agents in Danish ICUs 1996/97. A national survey. *Intensive Care Med* 1999; **25**: 186–91

19 Lloyd GG. Psychological problems and the intensive care unit. *Br Med J* 1993; **307**: 458–9

20 Meyer TJ, Eveloff SE, Bauer MS, Schwartz WA, Hill NS, Millman RP. Adverse environmental conditions in the respiratory and medical ICU settings. *Chest* 1994; **105**: 1211–16

21 Schwab RJ. Disturbances of sleep in the intensive care unit. *Crit Care Clin* 1994; **10**: 681–94

22 Koepke JP. Effect of environmental stress on neural control of renal function. *Mineral Electrolyte Metab* 1989; **15**: 83–7

23 Roth-Isigkeit A, Brechmann J, Dibbelt L, Sievers HH, Raasch W, Schmucker P. Persistent endocrine stress response in patients undergoing cardiac surgery. *J Endocrinol Invest* 1998; **21**: 12–19

24 Bonica JJ. Importance of effective pain control. *Acta Anaesthesiol Scand Suppl* 1987; **85**: 1–16

25 Lewis KS, Whipple JK, Michael KA, Quebbeman EJ. Effect of analgesic treatment on the physiological consequences of acute pain. *Am J Hosp Pharm* 1994; **51**: 1539–54

26 Burns AM, Shelly MP, Park GR. The use of sedative agents in critically ill patients. *Drugs* 1992; **43**: 507–15

27 Van der Linden P, Vincent JL. The effects of sedative agents. In: Edwards D, Shoemaker E, Vincent JL, eds. *Oxygen Transport: Principles and Practice.* London: Baillière Tindall, 1993; 209–225.

28 Durbin CG Jr. Sedation in the critically ill patient. *New Horiz* 1994; **2**: 64–74

29 Bosscha K, Nieuwenhuijs VB, Vos A, Samsom M, Roelofs JM, Akkermans LM. Gastrointestinal motility and gastric tube feeding in mechanically ventilated patients. *Crit Care Med* 1998; **26**: 1510–17

30 Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; **114**: 541–8

31 Cammarano WB, Pittet JF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* 1998; **26**: 676–84

32 Tung A, Rosenthal M. Patients requiring sedation. *Crit Care Clin* 1995; **11**: 791–803

33 Merriman HM. The techniques used to sedate ventilated patients. A survey of methods used in 34 ICUs in Great Britain. *Intensive Care Med* 1981; **7**: 217–24

34 Watling SM, Dasta JF, Seidl EC. Sedatives, analgesics, and paralytics in the ICU. *Ann Pharmacother* 1997; **31**: 148–53

35 Young C, Knudsen N, Hilton A, Reves JG. Sedation in the intensive care unit. *Crit Care Med* 2000; **28**: 854–66

36 Snellen F, Lauwers P, Demeyere R, Byttebier G, Van Aken H. The use of midazolam versus propofol for short-term sedation following coronary artery bypass grafting. *Intensive Care Med* 1990; **16**: 312–16

37 Sanchez IRJ, Caballero-Cubedo RE, Perez-Vela JL, Ambros-Checa A, Cantalapiedra-Santiago JA, Alted-Lopez E. Propofol versus midazolam: safety and efficacy for sedating the severe trauma patient. *Anesth Analg* 1998; **86**: 1219–24

38 Armstrong DK, Crisp CB. Pharmacoeconomic issues of sedation, analgesia, and neuromuscular blockade in critical care. *New Horiz* 1994; **2**: 85–93

39 Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *J Am Med Assoc* 2000; **283**: 1451–9

40 Sun X, Weissman C. The use of analgesics and sedatives in critically ill patients: physicians' orders versus medications administered. *Heart Lung* 1994; **23**: 169–76

41 Gilliland HE, Prasad BK, Mirakhur RK, Fee JP. An investigation of the potential morphine sparing effect of midazolam. *Anaesthesia* 1996; **51**: 808–11

42 Carrasco G, Cabre L, Sobrepere G, *et al.* Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting. *Crit Care Med* 1998; **26**: 844–51

43 Park GR. Drugs used to make critically ill patients comfortable. *Curr Opin Crit Care* 1999; **5**: 249–50

44 Vincent JL. Communication in the ICU. *Intensive Care Med* 1997; **23**: 1093–8

45 Ramsay MAE, Savage TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone–alphadolone. *Br Med J* 1974; **ii**: 656–9

46 Chernik DA, Gillings D, Laine H, *et al.* Validity and reliability of Observer's Assessment of Alertness/Sedation Scale. Study with intravenous midazolam. *J Clin Psychopharmacol* 1990; **10**: 244–7

47 Wang DY, Pomfrett CJ, Healy TE. Respiratory sinus arrhythmia: a new, objective sedation score. *Br J Anaesth* 1993; **71**: 354–8

48 Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation–Agitation Scale for adult critically ill patients. *Crit Care Med* 1999; **27**: 1325–9

49 Devlin JW, Boleski G, Mlynarek M, *et al.* Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999; **27**: 1271–5

50 Detriche O, Berre J, Massaut J, Vincent JL. The Brussels sedation scale: use of a simple clinical sedation scale can avoid excessive sedation in patients undergoing mechanical ventilation in the intensive care unit. *Br J Anaesth* 1999; **83**: 698–701

51 Hansen-Flaschen J, Cowen J, Polomano RC. Beyond the Ramsay scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Crit Care Med* 1994; **22**: 732–3

52 Brook AD, Ahrens TS, Schaiff R, *et al.* Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; **27**: 2609–15

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Effects of desflurane on cerebral autoregulation

N. M. Bedforth, K. J. Girling, H. J. Skinner and R. P. Mahajan*

University Department of Anaesthesia, Queen's Medical Centre and City Hospital, Nottingham NG7 2UH, UK

**Corresponding author*

The aim of this study was to determine the effects of desflurane, at 1 and 1.5 MAC, on cerebral autoregulation. Data were analysed from eight patients undergoing non-neurosurgical procedure. The blood flow velocity in the middle cerebral artery was measured by transcranial Doppler ultrasound and cerebral autoregulation was assessed by the transient hyperaemic response test. Partial pressure of the end-tidal carbon dioxide ($P_{E'_{CO_2}}$) and mean arterial pressure were measured throughout the study. Anaesthesia was induced with propofol and was maintained with desflurane at end-tidal concentrations of 7.4% (1 MAC) or 10.8% (1.5 MAC). The order of administration of the desflurane concentrations was determined randomly and a period of 15 min was allowed for equilibration at each concentration. The transient hyperaemic response tests were performed before induction of anaesthesia and after equilibration with each concentration of desflurane. An infusion of phenylephrine was used to maintain pre-induction mean arterial pressure and ventilation was adjusted to maintain the pre-induction value of $P_{E'_{CO_2}}$ throughout the study. Two indices derived from the transient hyperaemic response test (the transient hyperaemic response ratio and the strength of autoregulation) were used to assess cerebral autoregulation. Desflurane resulted in a marked and significant impairment in cerebral autoregulation; at concentrations of 1.5 MAC, autoregulation was almost abolished.

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Desflurane is a relatively new volatile anaesthetic agent with a low blood:gas solubility coefficient, a physical property that allows rapid alterations in depth of anaesthesia. It has been shown to cause a dose-dependent decrease in cerebral vascular resistance.[1 2]

To our knowledge, only one study has examined the effects of desflurane on cerebral autoregulation. Strebel and colleagues[3] showed that desflurane, at concentrations greater than 0.5 MAC, produced a dose-dependent impairment in both static and dynamic cerebral autoregulation. However, in that study, 70% nitrous oxide was used as the background anaesthetic, on the assumption that it had minimal effects on cerebral autoregulation. We have shown that nitrous oxide can have profound effects on cerebral autoregulation,[4] and that its presence can modify the effects of sevoflurane on cerebral autoregulation.[5] Therefore, the results of the study by Strebel and colleagues[3] could have been confounded by the presence of nitrous oxide.

In the present study, we aimed to evaluate the effects of desflurane, when used as the sole inhalation anaesthetic, on cerebral autoregulation as assessed by the transient hyperaemic response test (Fig. 1).

Methods

After obtaining approval from the Hospital Ethics Committee and written, informed consent, eight patients, ASA 1 or 2, aged between 18 and 40 yr and undergoing elective non-neurosurgical procedures, were recruited. Patients were excluded if they were overweight, had any evidence of cerebrovascular or neurological disease or if they were taking any vasoactive medications.

Study set-up

All patients were studied in the supine position with the head resting on a pillow. The study was performed in the anaesthetic room before surgery.

A standardized procedure for the measurement of flow velocity in the middle cerebral artery was followed. The left

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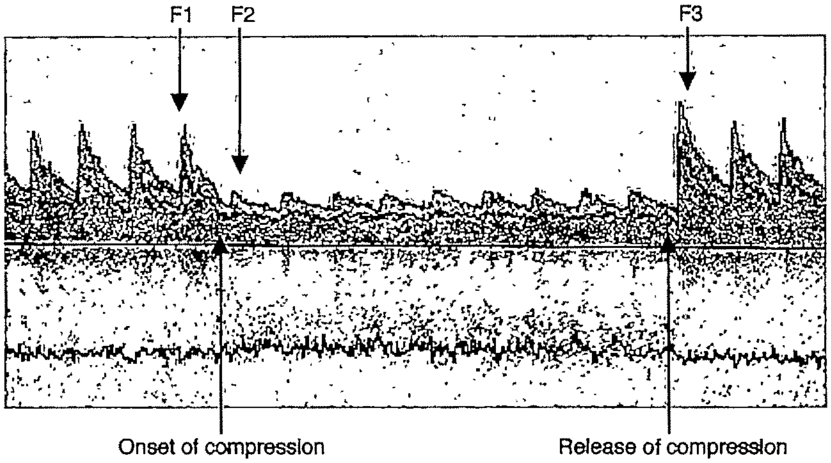

Fig 1 Middle cerebral artery flow velocity during a typical transient hyperaemic response test. The flow velocity decreases suddenly at the onset of compression of ipsilateral common carotid artery and, if the autoregulation is intact, shows hyperaemic response at the release of compression. The pulse wave form immediately before the onset of compression (F1), immediately after the onset of compression (F2) and that immediately after the release of compression (F3) are taken for calculating the transient hyperaemic response ratio and strength of autoregulation.

middle cerebral artery was insonated through the temporal window using a 2 MHz transcranial Doppler ultrasound probe (SciMed QVL 120, SciMed, Bristol, UK). The identity of the flow velocity waveform in the middle cerebral artery was confirmed using standard criteria.[6 7] The position of the transcranial Doppler probe was fixed using a headband to ensure a constant angle of insonation throughout the study. The flow velocity was recorded continuously on digital audiotape for subsequent analysis using specific software (SciMed, Bristol, UK). I.v. access was secured and monitoring was initiated using an electrocardiogram, non-invasive arterial pressure measurement and pulse oximetry. Mean arterial pressure was measured at 2-min intervals and the partial pressure of end-tidal carbon dioxide ($P\text{E}'_{\text{CO}_2}$) was measured continuously using a Marquette Tramscope (Marquette Electronics, Milwaukee, USA).

After an initial period of rest of approximately 10 min, each patient was subjected to repeated left common carotid artery compressions of 10 s duration for the baseline measurements at 2-min intervals until a test fulfilling the predetermined criteria (see below) was obtained. Mean arterial pressure and $P\text{E}'_{\text{CO}_2}$ were recorded immediately before every transient hyperaemic response test.

Following the pre-induction test of cerebral autoregulation, anaesthesia was induced using a target-controlled infusion of propofol set to a target blood concentration of 8 μg ml^{-1}. Neuromuscular block was produced by vecuronium 0.1 mg kg^{-1}. The trachea was intubated and the lungs were mechanically ventilated with 100% oxygen. Ventilation was controlled to maintain $P\text{E}'_{\text{CO}_2}$ at the pre-induction (±0.1 kPa) level. The infusion of propofol was stopped after tracheal intubation had been achieved and administration of desflurane was started. Two end-tidal concentrations of desflurane, 7.4% (1 MAC) and 10.8% (1.5 MAC), were studied in random order. The transient hyperaemic response tests were repeated allowing a 15-min equilibration period after achieving a constant end-tidal concentration of desflurane, and after ensuring that the estimated blood concentration of propofol was below 1.5 μg ml^{-1}. Phenylephrine was used to maintain mean arterial pressure at the pre-induction (±10%) level throughout the study.

Transcranial Doppler data

The methods of processing the transcranial Doppler data have been described previously.[4 5 8] The criteria for accepting a transient hyperaemic response test included:

(i) sudden and maximal decrease in flow velocity at the onset of common carotid artery compression;

(ii) stable heart rate and power of reflected Doppler signal during compression; and

(iii) absent flow transients after release of compression (associated with inertial or volume compliance).[9]

For analysis, the flow velocity waveform in the middle cerebral artery immediately before the compression (F1), the first waveform immediately following compression (F2), and that immediately after release (F3), were selected (Fig. 1). The time-averaged mean of the outer envelope of the flow velocity was used for analysis. The power of the Doppler signal was recorded as an indicator of any change in the diameter of the middle cerebral artery during the transient hyperaemic response test. The change in power was considered significant if, at any stage, it was outside the range recorded within 10 s of the baseline measurement.

Calculations

Two indices of cerebral autoregulation were derived—the transient hyperaemic response ratio and the strength of autoregulation, calculated as follows:

Table 1 Mean (SD) values of compression ratio (CR), middle cerebral artery (MCA) flow velocity (FV), transient hyperaemic response ratio (THRR) and strength of autoregulation (SA) before induction of anaesthesia, and after equilibration with end-tidal concentrations of desflurane of 7.4 and 10.8%

	Baseline	**Desflurane 7.4%**	**Desflurane 10.8%**	ANOVA
CR (%)	34.4(6.6)	40.1 (8.0)	42.4 (5.9)	n.s.
MCA FV (cm s^{-1})	63.56 (6.52)	71.26 (18.68)	76.45 (14.65)	n.s.
THRR	1.38 (0.12)	1.13 (0.15)	1.04 (0.04)	$P<0.001$
SA	1.03 (0.09)	0.83 (0.13)	0.76 (0.09)	$P<0.001$

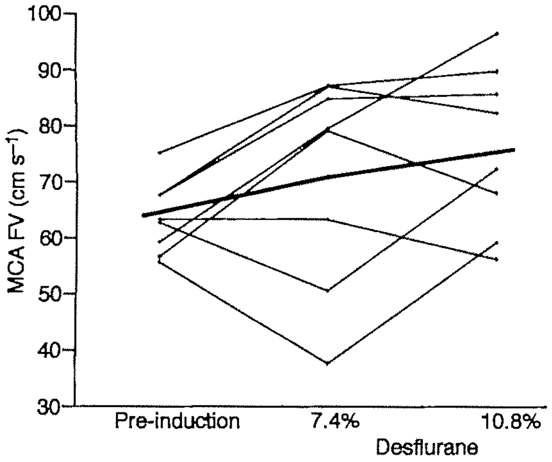

Fig 2 Middle cerebral artery (MCA) flow velocity (FV) for the eight patients before induction of anaesthesia and during anaesthesia maintained with desflurane at end-tidal concentrations of 7.4 and 10.8%. The thin lines show changes for each individual and the thick line shows mean changes. The changes were insignificant.

transient hyperaemic response ratio[10,11] = F3/F1

strength of autoregulation[8,12] = (F3.P2)/(MAP.F1), where MAP is the mean arterial pressure.

The P2 is the estimated pressure in the middle cerebral artery at the onset of compression and is derived using the formula: P2 = MAP.F2/F1 or the value of 60 mm Hg (the assumed lower limit of autoregulation), whichever is the greater.[8,12]

The magnitude of decrease in the flow velocity during compression, the compression ratio, was calculated from the formula:[10,11]

Compression ratio (%) = (F1–F2)×100/F1

Statistics

Pooled data from subjects involved in studies in our department indicate that the mean (SD) value for transient hyperaemic response ratio is 1.33 (0.09) and for the strength of autoregulation is 0.96 (0.07) under normal physiological condition.[4,5,8,11,13] A change of >2 SD in the value of strength of autoregulation was considered significant. We calculated that eight subjects would be required to reject our null hypothesis for $\alpha<0.05$ and that for $\beta>0.95$

Analysis of variance (ANOVA) for repeated measurements was used to compare the values of flow velocity, compression ratio, transient hyperaemic response ratio, and strength of autoregulation after each intervention. Significance was assumed at P values <0.05.

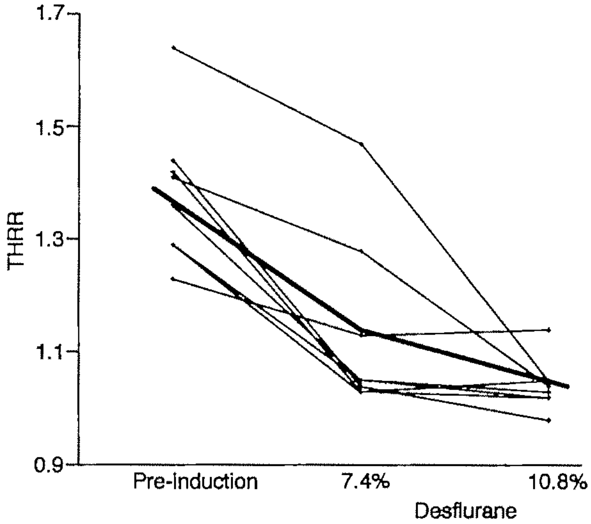

Fig 3 The transient hyperaemic response ratio (THRR) for the eight patients before induction of anaesthesia and during anaesthesia maintained with desflurane at end-tidal concentrations of 7.4 and 10.8%. The thin lines show changes for each individual and the thick line shows mean changes. The changes were significant ($P<0.001$).

Results

Four male and four female patients were recruited. The mean (SD) age was 29 (5) yr and weight was 73.5 (7.5) kg. At each stage, up to three tests were performed to obtain one test that fulfilled all the criteria described in the Methods section.

Changes in compression ratio and flow velocity were not significant (Table 1). Figures 2–4 show the changes in flow velocity, transient hyperaemic response ratio, and strength of autoregulation for the eight subjects. Both transient hyperaemic response ratio and strength of autoregulation were decreased significantly under desflurane anaesthesia.

Discussion

In this study, desflurane significantly impaired cerebral autoregulation. Based on studies of changes in this transient hyperaemic response ratio and strength of autoregulation

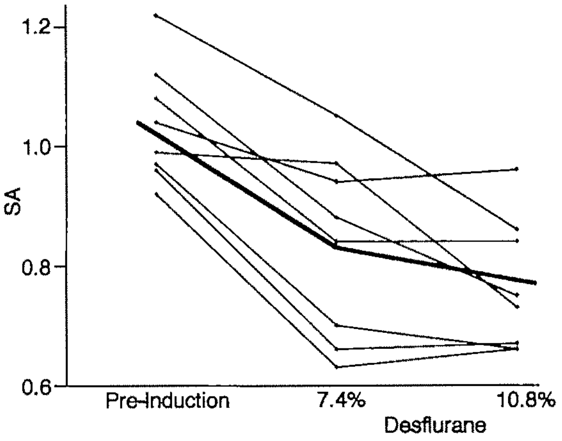

Fig 4 The strength of autoregulation (SA) for the eight patients before induction of anaesthesia and during anaesthesia maintained with desflurane at end-tidal concentrations of 7.4 and 10.8%. The thin lines show changes for each individual and the thick line shows mean changes. The changes were significant ($P<0.001$).

induced by carbon dioxide,[8] or the transient hyperaemic response ratio and rate of regulation assessed by the thigh-cuff method,[10] it can be inferred that a change of 0.2 (>2 SD) in transient hyperaemic response ratio or of 0.16 (>2 SD) in strength of autoregulation would indicate a significant effect on autoregulation. The mean changes induced by 10.8% desflurane in our study were well above these values. At an end-tidal concentration of 10.8% of desflurane, the mean (SD) transient hyperaemic response ratio was 1.04 (0.04) and the mean (SD) strength of autoregulation was 0.76 (0.09). These values suggest that at 1.5 MAC of desflurane most patients had poor or abolished autoregulation. It has been shown that transient hyperaemic response ratio of less than 1.09 indicates absent autoregulation.[14] Seven out of eight patients in this study had a transient hyperaemic response ratio <1.09 at 10.8% desflurane.

The details of the modelling of cerebral autoregulation using the transient hyperaemic response test have been published previously.[8 10–12 14 15] The decrease in the perfusion pressure in the middle cerebral artery at the onset of carotid artery compression provokes the autoregulatory vasodilatation in the territory of the middle cerebral artery. Release of compression allows the perfusion pressure to return to baseline but because of the reduced vascular resistance the flow velocity overshoots the baseline value (the hyperaemic response). In theory the hyperaemic response can be affected by the changes in both the gradient and the limits of the autoregulatory plateau.[8 12 15] In practice, however, it is not possible to differentiate between the two effects. In the past, the transient hyperaemic response test has been used to assess the effects of carbon dioxide, nitrous oxide, sevoflurane and propofol on cerebral autoregulation.[4 5 8 13]

According to theoretical modelling, as an index of autoregulation, the transient hyperaemic response ratio is likely to be affected by changes in mean arterial pressure or compression ratio; strength of autoregulation is unlikely to be affected by these experimental factors.[11 12 15] However, when the mean arterial pressure and compression ratio remain unchanged on repeated measurements, as in this study, there is likely to be little difference between the findings of the two indices.

Strebel and colleagues,[3] using static and thigh-cuff methods, examined the effects of desflurane on cerebral autoregulation with nitrous oxide in the background; in this study, desflurane impaired cerebral autoregulation in a dose-dependent fashion. At 0.5 MAC, the autoregulation was delayed but preserved; at 1 and 1.5 MAC it was significantly impaired. After having shown that nitrous oxide *per se* can impair cerebral autoregulation,[4] and also that it can influence the effect of sevoflurane on cerebral autoregulation,[5] we felt it necessary to study desflurane in the absence of any possible confounding effects of nitrous oxide. However, the results of the present study using 1 and 1.5 MAC of desflurane are similar to those of Strebel and colleagues[3] suggesting that desflurane in these concentrations is detrimental to cerebral autoregulation whether it is used with or without nitrous oxide.

In the present study, propofol was used for induction of anaesthesia but the measurements for cerebral autoregulation were made only after its predicted blood concentration was below 1.5 mg ml^{-1}. In previous studies, infusion of anaesthetic doses of propofol did not impair cerebral autoregulation.[3 13]. Therefore, it is unlikely that any small quantities of propofol remaining in the blood during equilibration with desflurane would have had a significant effect on the results of this study.

We found that the mean flow velocity in the middle cerebral artery tended to increase during inhalation of desflurane, but this increase failed to reach statistical significance. We noted a large between-subject variability of these measurements. Previous studies suggest that desflurane can increase cerebral blood flow by dilating the cerebral blood vessels.[1 2] It is well known that reduced cerebrovascular resistance, including that caused by hypercapnia, causes a significant shortening of the autoregulatory plateau with a higher lower limit and a lower upper limit.[16] This may partly explain why both transient hyperaemic response ratio and strength of autoregulation were significantly affected in our study, indicating impaired cerebral autoregulation secondary to vasodilatation caused by desflurane. However, as discussed earlier,[8 12] the transient hyperaemic response test cannot determine whether the primary effect of an agent (desflurane in this study) is on the width or the gradient of the autoregulatory plateau.

The present study has a number of limitations. Changes in flow velocity measured using transcranial Doppler reflect changes in blood flow only if the diameter of the insonated vessel remains constant. Matta and Lam[17] presented data that suggest that desflurane has a minimal effect on the diameter of the middle cerebral artery. In addition, modest changes in arterial pressure and carbon dioxide partial pressure have been shown to have minimal effects on the middle cerebral artery diameter.[18] In the present study, the reflected power of the Doppler signal remained unchanged during the transient hyperaemic response tests, suggesting that the changes in the diameter of the middle cerebral artery, if any, were insignificant.[19]

The present study was conducted in patients with no intracranial pathology, who were maintained normocapnic and normotensive. Therefore, the clinical conditions were different from those of patients undergoing neurosurgical procedures. Further studies are required to determine the interactions between desflurane and other techniques, such as hyperventilation, which influence cerebral blood flow and autoregulation, in order to define the clinical conditions during which desflurane may adversely affect cerebral haemodynamics.

In conclusion, we have shown that desflurane, at concentrations of 1 MAC or above, causes a significant impairment in cerebral autoregulation.

References

1 Lutz LJ, Milde JH, Milde LN. The cerebral functional, metabolic and hemodynamic effects of desflurane in dogs. *Anesthesiology* 1990; **73**: 125–31

2 Ornstein E, Young WL, Ostapkovich N, Prohovnik I, Stein BM. Comparative effects of desflurane and isoflurane on cerebral blood flow. *Anesthesiology* 1991; **75**: A209

3 Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static autoregulation during isoflurane, desflurane and propofol anesthesia. *Anesthesiology* 1995; **83**: 66–76

4 Girling KJ, Cavill G, Mahajan RP. The effects of nitrous oxide and oxygen on transient hyperemic response in human volunteers. *Anesth Analg* 1999; **89**: 175–80

5 Bedforth NM, Girling K, Harrison JM, Mahajan RP. The effects of sevoflurane and nitrous oxide on middle cerebral artery blood flow velocity and transient hyperaemic response. *Anesth Analg* 1999; **89**: 170–4

6 Aaslid R. The Doppler principle applied to measurement of blood flow velocity in central arteries. In: Aaslid R, ed. *Transcranial Doppler Ultrasonography*. Vienna: Springer-Verlag, 1986

7 Aaslid R, Lindegaard K-F, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45–52

8 Mahajan RP, Cavill G, Simpson EJ. Reliability of the transient hyperaemic response test in detecting changes in cerebral autoregulation induced by graded variations in end-tidal carbon dioxide. *Anesth Analg* 1998; **87**: 843–9

9 Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard KF. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke* 1991; **22**: 1148–54

10 Smielewski P, Czosnyka M, Kirkpatrick P, McEroy H, Rutkowska H, Pickard JD. Assessment of cerebral autoregulation using carotid artery compression. *Stroke* 1996; **27**: 2197–203

11 Cavill G, Simpson EJ, Mahajan RP. Factors affecting the assessment of cerebral autoregulation using the transient hyperaemic response test. *Br J Anaesth* 1998; **81**: 317–21

12 Mahajan RP, Cavill G, Simpson EJ, Hope DT. Transient hyperaemic response: a quantitative assessment. In: Klingelhofer J, Bartels E, Ringelstein EB, eds. *New Trends in Cerebral Haemodynamics and Neurosonology*. Amsterdam: Elsevier Science B.V., 1997: 618–23

13 Harrison JM, Girling KJ, Mahajan RP. The effects of target controlled infusion of propofol on the transient hyperaemic response and carbon dioxide reactivity in middle cerebral artery. *Br J Anaesth* 1999; **83**: 839–45

14 Smielewski P, Czosnyka M, Iyer V, Piechnik S, Whitehouse H, Pickard J. Computerised transient hyperaemic response test–a method for the assessment of cerebral autoregulation. *Ultrasound Med Biol* 1995; **21**: 599–611

15 Czosnyka M, Pickard J, Whitehouse H, Piechnik S. The hyperaemic response to a transient reduction in cerebral perfusion pressure: a modelling study. *Acta Neurochir* 1992; **115**: 90–7

16 Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161–92

17 Matta BF, Lam AM. Isoflurane and desflurane do not dilate the middle cerebral artery appreciably (abstract). *Br J Anaesth* 1995; **74**: 486P

18 Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993; **32**: 737–42

19 Busija DW, Heistad DD, Marcus ML. Continuous measurements of cerebral blood flow in anesthetised cats and dogs. *Am J Physiol* 1981; **241**: H228–34

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Association of airway obstruction, sleep, and phasic abdominal muscle activity after upper abdominal surgery†

M. Q. Rahman[1], R. N. Kingshott[2], P. Wraith[2], W. H. Adams[3] and G. B. Drummond[1]*

[1]Departments of Anaesthetics and [2]Sleep Medicine, Royal Infirmary, Edinburgh EH3 9YW, UK and [3]Medical Statistics Unit, Public Health Sciences, Edinburgh University, Edinburgh EH8 9AG, UK

**Corresponding author*

We recorded nasal gas flow, sleep stage, and abdominal muscle EMG pattern in 11 patients throughout the night after abdominal surgery, to examine the association between phasic activity of the abdominal muscles, sleep stage, and flow disturbance. We used a miniaturized data logging system, and obtained satisfactory records in eight patients. The data were divided into 30-s epochs. Each epoch was classified as either awake or asleep. The epochs were also classified for the presence of phasic activity in the external oblique abdominal muscle, and for evidence of airway obstruction. Association between these features was tested by a quasi likelihood log linear model. Values given are median (quartiles) for the eight subjects. Sleep occurred for 62 (46–69)% of the study time. During sleep, inspiratory flow was normal for 69 (48–81)% of the time, whereas during wakefulness, the flow pattern was normal for 51 (28–77)% of the time. Phasic activity was present 16 (12–25)% of the time during sleep and 24 (19–37)% of the time during wakefulness ($P<0.001$). In the awake state, when breathing was normal, phasic activity was present 16 (11–30)% of the time. When breathing was obstructed, phasic activity was present 38 (25–44)% of the time ($P<0.001$). These surprising findings suggest that sleep may be seriously disturbed by airway obstruction, so that a stable sleep state is not reached. We could not confirm previous findings that disturbed breathing in post-operative patients only occurs during sleep.

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In patients who have had abdominal surgery, frequent episodes of hypoxaemia have been reported during sleep in the night after surgery.[1] These episodes were associated with abnormal chest wall movements consistent with the presence of airway obstruction. We observed abdominal muscle activity in patients after upper abdominal surgery, with a phasic pattern of greater activity during expiration.[2] This activity is significantly associated with airway obstruction and abnormal chest wall movements,[3] has a marked effect on abdominal pressure,[4] and is likely to reduce functional residual capacity and worsen gas exchange. However, this pattern of activity is not constant, and periods occur when the muscles are tonically active. We considered that because airway obstruction has been associated with both episodic hypoxaemia and sleep, there should be an association between airway obstruction, sleep, and phasic muscle activity. We designed an observational study to examine the relationship, considering it likely that during sleep, as during anaesthesia,[5] abdominal muscle activity would be phasic.

Methods

The study was approved by the relevant subcommittee of the Health Board Ethics Committee. On the day before surgery, we asked patients to participate and obtained written informed consent. After surgery, the patients were seen in the recovery area and the following electrodes and sensors were applied. Sleep was monitored by electroencephalography (EEG) with silver/silver chloride electrodes applied at scalp sites Cz-Pz and C3-C4, by electrooculography (EOG) using disposable gel electrodes above and lateral to the eyes, and by submental electromyography (EMG). We used a pair of similar disposable gel electrodes placed in the right upper quadrant of the abdomen to measure external oblique abdominal muscle EMG, another pair of gel electrodes to measure ECG, and placed a strain gauge sensor round the lower rib cage to measure chest wall excursions. The strain gauge also carried a

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position sensor to indicate the dependent side of the patient. We placed a nasal pressure cannula (ProTek airflow sensor) (similar to a very narrow nasal oxygen cannula) at the nostrils and connected this to a miniature differential pressure transducer (Gaeltec 3EA). All the devices were taped firmly in place with adhesive dressings, and the cables were led away in a single bundle from the patient's shoulder to a miniature data logging harness at the head of the bed. The submental EMG was filtered between 22 and 90 Hz with a 50 Hz notch, and the other sleep stage signals between 0.3 and 35 Hz. After the patient had returned to the ward, and was stable and comfortable, the recording was started with a portable polysomnographic recording system (Embla), and continued for 14 h.

The patients were nursed in a multi-bedded high dependency unit with a staff provision of one nurse for two patients. No special precautions were taken to ensure that the ward was quiet or to adjust the level of lighting, but the ward lights are kept low during the night hours. We did not have ethical permission to modify clinical practice in any way, and anaesthesia during surgery, and analgesia after the operation, were according to the preference of the anaesthetist involved. However, in all cases anaesthesia involved premedication with temazepam orally, i.v. induction of anaesthesia with propofol, neuromuscular block with either atracurium or vecuronium, and nitrous oxide and isoflurane to maintain anaesthesia. In five patients, a thoracic epidural catheter was placed at the start of anaesthesia so that post-operative analgesia could be provided using a continuous infusion of a mixture of bupivacaine (0.125%) with either fentanyl or diamorphine. In the other eight patients, analgesia was provided with a patient controlled injection device programmed to deliver morphine 2 mg i.v. with a 5 min lockout period between demands.

After overnight recording, the data from the portable logging system were downloaded onto a personal computer for analysis. For each patient, three separate passes through the system were needed. These passes were to determine the presence or absence of sleep, of phasic or tonic abdominal muscle activity, and of airway obstruction. Each of the three passes through the data was performed with the other traces hidden so that each trace was scored independently. The scorer who had been in contact with the patient was blinded to the identity of the data. Each coded tracing was analysed using the same synchronized 30 s epochs. In all cases, the operator classified each epoch if the feature was either present, absent, or could indicate 'unsure' if a clear distinction between the states could not be drawn. These features were sleep, phasic activity, and airway obstruction, depending on the variable being inspected. Sleep was determined by standard criteria.[6] Each epoch was considered either wake or sleep if either state occupied more than 15 s (Fig. 1). Abdominal muscle activity was classified as phasic if a recognizable phasic pattern was present, with a frequency between 0.1 and 0.4 Hz, at any time during the 30 s (Fig. 2). Respiration was considered abnormal if there was any change in the clear inspiratory and expiratory pattern, or if the smooth domed appearance of the inspiratory wave was reduced in amplitude with a 'flow limitation' pattern (Fig. 3).[7 8] After these sets of signals had been separately classified, the code was broken and the association between sleep stage, phasic activity, and abnormal nasal flow analysed. Each patient's time was successively categorized in three ways: first, according to sleep state (awake/asleep); then according to the pattern of breathing (clear/obstructed); and finally according to abdominal muscle action (phasic/tonic).

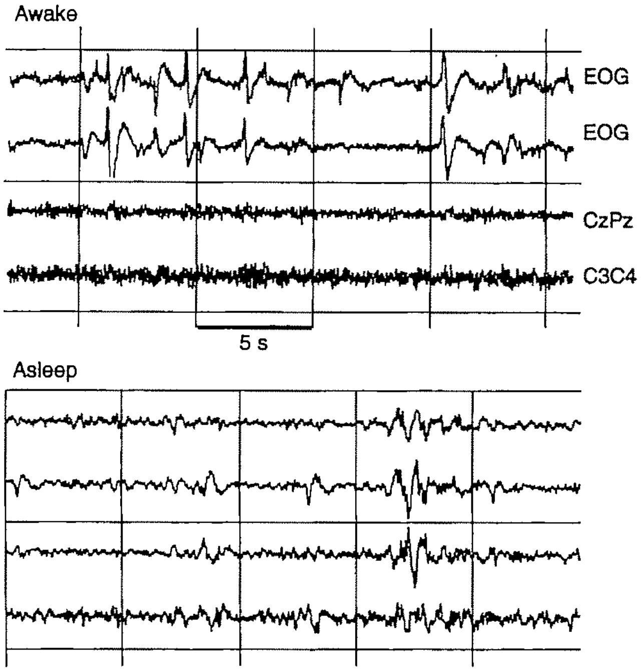

Fig 1 Part of polysomnogram tracing from a typical patient with awake and sleep pattern. EOG: electrooculogram; CzPz and C3C4: EEG traces. The awake trace shows low voltage high frequency activity and the sleep trace shows K complexes and sleep spindles.

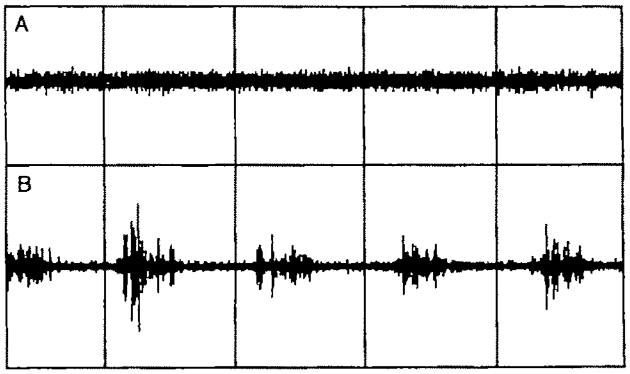

Fig 2 Abdominal EMG patterns. (A) Tonic, (B) phasic. Vertical lines indicate 5 s.

The association between these categories was studied using a quasi likelihood log linear model.[9] Other two-way associations were explored by the chi-squared test, with Minitab version[10] run on a personal computer. All values for the patient data are given as median and quartiles for the eight subjects, unless otherwise stated.

Results

We recruited 13 patients. The planned surgery was changed in two of them, and in the remaining 11 patients, the recording of the nasal flow signal was technically inadequate in two, and in one subject both EEG leads became disconnected. We, therefore, obtained technically satisfactory recordings in eight patients with 14.2 (13.4–14.6) h of recording, and 95 (93–98)% of these recordings were classifiable for all three channels. In the remainder of the recording, one or more signals had to be classified as 'uncertain'. The most frequently unclassifiable signal was the abdominal EMG, which was classified as uncertain for nearly 3% of the recording time.

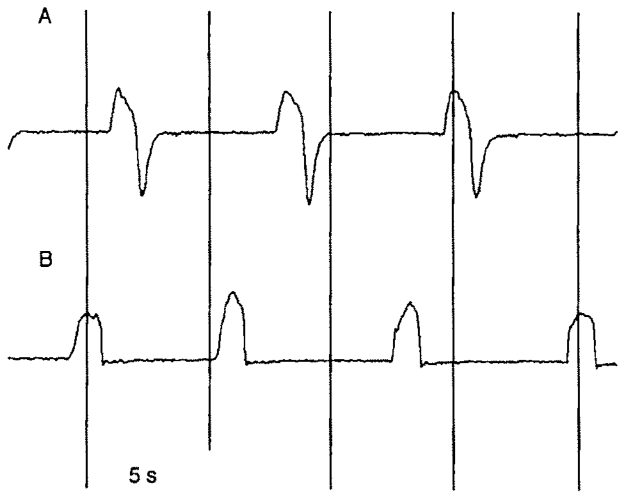

Fig 3 Examples of nasal flow pattern during (A) normal breathing and (B) obstructed inspiration showing absence of expiratory flow and flow limitation during inspiration. Vertical lines indicate 5 s.

The mean age of the patients was 39 yr (range 24–58), height 173 (SD 14) cm and weight 77 (15) kg. Four of the patients were male and five patients had thoracic epidurals. The other patients had analgesia with patient controlled i.v. morphine. The median total dosage of morphine in these patients, during and after surgery, up to the end of the study period, was 51 (15–90) mg. Most of the patients had operations for partial hepatic resection or pancreatic surgery.

The relative duration of each study period, spent in the different states, is shown in Table 1. The interactions between these states that could be studied are given in Table 2. The first two lines of this table present and test the *a priori* hypothesis, but we first present some of the more general results.

Patients were awake for 38 (31–58)% of the study period, and breathed normally for 54 (46–68)% of the time. While the patients were awake, the breathing was normal for 51 (28–77)% of the time.

Only one patient showed slow wave sleep (stage 3 or 4) and none showed any REM sleep. When the patients were asleep, breathing was normal for 69 (48–81)% of the time. In six of the patients, breathing was normal for more of the time during sleep than during wakefulness.

Phasic abdominal muscle activity could be detected in all except one of the patients at some time in the recording period, and was not clearly altered in those patients who had epidural anaesthesia although there could have been a decrease in the amplitude of the action potentials in these patients. Phasic abdominal muscle activity was present for 25 (18–31)% of the duration of the recordings. Phasic activity was less common when the patients were asleep. During sleep, activity was phasic for only 16 (12–25)% of the time, whereas during wakefulness, phasic activity was present for 24 (19–37)% of the time.

Table 1 Percentage of classifiable recording spent in different conditions

Sleep state	Awake				Asleep			
Breathing	Normal		Obstructed		Normal		Obstructed	
Abdominal EMG subject	Tonic	Phasic	Tonic	Phasic	Tonic	Phasic	Tonic	Phasic
1	14	2	29	10	29	7	6	3
2	2	0	24	7	17	5	40	5
3	16	3	25	15	21	11	5	3
4	5	6	14	17	17	4	34	3
5	31	9	8	5	38	5	4	0
6	10	10	3	6	52	9	8	3
7	24	1	5	1	39	1	27	2
8	11	0	2	1	44	0	11	30
1st Quartile	9	1	4	4	20	3	6	3
Median	12	3	11	7	34	5	10	3
3rd Quartile	18	7	24	11	40	7	28	4

Table 2 Likelihoods of significant interactions between observed conditions. The first two rows represent the *a priori* hypothesis

		Interaction between:	**Quasi likelihood ratio test**			
			Λ	SE (Λ)	**Chi-squared, 1 df**	**Probability**
Wake	Breathing	Abdominal EMG	0.553	0.212	6.81	<0.001
Sleep	Breathing	Abdominal EMG	0.346	0.283	1.26	n.s.
Clear	Sleep state	Abdominal EMG	–0.533	0.2903	7.1	<0.001
Obstructed	Sleep state	Abdominal EMG	–0.742	0.247	9.32	<0.001
Tonic	Sleep state	Breathing	–0.231	0.222	1.07	n.s.
Phasic	Sleep state	Breathing	–0.691	0.259	7.23	<0.001

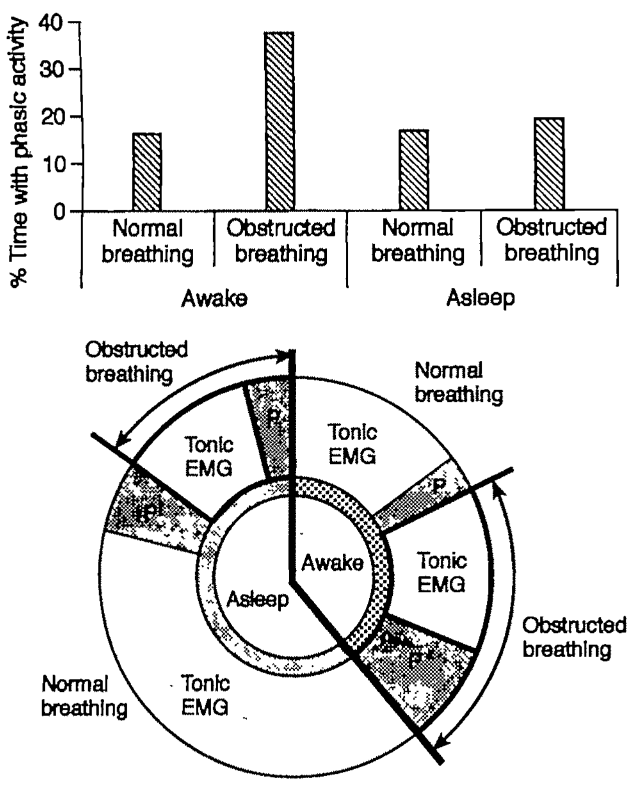

Fig 4 Median proportion of time spent in each condition by the patients studied. P indicates time when phasic EMG was present. The greater proportion of phasic activity during obstructed breathing, particularly during wakefulness, can be seen.

There were significant interactions between sleep state, breathing pattern, and phasic activity of the abdominal muscles. When awake, the patients had significantly more phasic abdominal muscle activity when the nasal airflow was obstructed ($P<0.001$), but there was no significant interaction between the pattern of abdominal activity and obstruction during sleep. When the breathing was normal, there was less phasic abdominal muscle action during sleep ($P<0.001$) (Fig. 4). One patient (number 8) had an unusually large proportion of phasic activity present during obstructed breathing while asleep. This patient was receiving an epidural infusion of 0.125% bupivacaine, which contained clonidine 0.6 $\mu g\ ml^{-1}$.

Discussion

This observational study was intended to answer a single question and help direct further investigation of postoperative breathing difficulties. We found a highly significant relationship between airway obstruction and phasic abdominal activity, but we were surprised to find that this relationship was only present during wakefulness. In addition, we were surprised to find that abnormal breathing was more frequent during wakefulness. When Catley and colleagues[1] examined the relationship between episodes of hypoxaemia, breathing abnormalities, and sleep, they found that these episodes only occurred during sleep. On the basis of this past study and our clinical impressions, we expected to find abnormal breathing during periods of sleep. However, few workers, other than Catley and colleagues, have studied sleep state at the same time as respiratory disturbances in patients after surgery.

We used standard methods for measurement and ensured that the association we found was not affected by the possibility of bias, by conducting separate blinded classification of the three features. We have previously found measurement of respiratory flow with a nasal cannula system[10] to be simple and effective for periods of several hours[11] and the method has now been applied successfully for assessment of sleep disturbed breathing.[8 12 13]

The standard method for determination of sleep stage that we used has been defined in criteria that were accepted by consensus as standard in 1968. These criteria are the current standard in sleep labs and are well known and widely used. The transition between wake and stage 2 is relatively unequivocal, defined by simultaneous changes in EEG and EMG signals. There are few other criteria used for sleep definition, so the validity of these criteria has not been widely tested but they are reliable and generally accepted. Unfortunately, sleep classification is a skilled and 'labour intensive' task, needing individual inspection and classification of successive 30-s epochs of recording.

Our patients often appeared asleep after surgery and the nurses considered that they were asleep. Analysis of the EEG and submental EMG showed, however, that a large proportion of this time was in fact wakefulness. Data on the extent of sleep and the validity of different methods of assessment are scanty, but our observations support those of others. In a study using the same criteria,[14] patients similar to ours had an average nightly sleep duration of 2.5 h, which was estimated by the attendant nurses to be 7 h. Trained intensive care nurses are more accurate in this estimate, and assess the sleep state correctly on 73.5% of occasions, when observing medical ICU patients undergoing mechanical ventilation.[15]

These criteria for sleep may not be appropriate for patients receiving opioids. For example, the EEG frequencies that we noted during what was classified as wakefulness were often low. However, as there are no alternative widely used methods of staging, we chose to use the standard criteria. In addition, it is possible that we did not detect rapid and transient arousals, which are considered to be responsible for some of the symptoms found in patients with sleep-disordered breathing.

Finally, the recording of external oblique EMG is a simple and robust technique that we have used successfully in many post-operative patients. In the present study, it may have been affected by the presence of subclinical epidural motor block in some patients, although our patients showed no clinical evidence of abdominal weakness. Stimuli such as hypercapnia and elastic loads activate different abdominal muscles to different degrees. The external muscles, such as the external oblique, are less readily activated than inner muscles such as the transversus abdominis.[16] However, recording the activity of that muscle requires needle or wire electrodes, so we chose to study a muscle that can be assessed by surface electrodes, even though it gives a less sensitive indication of general expiratory abdominal activation. Despite this disadvantage, we still found a highly significant relationship.

Sleep quantity and quality were poor in our subjects, confirming previous studies of patients after surgery. Factors such as noise, frequent measurement of arterial pressure and other observations, pain, and some hormonal changes can reduce the capacity to attain deeper sleep.[17] There is some evidence in man that morphine can reduce the amounts of both slow wave and REM sleep.[18] Studies in cats suggest that this action involves a cholinergic pathway in the pontine reticular formation.[19 20] Despite the evidence that opioid analgesics disturb sleep, most empirical evidence is that patients receiving opioid analgesia are drowsy, have evidence of increased airway resistance or frank obstruction, and have repeated episodes of hypoxaemia attributable to obstructive as well as central apnoea.[21 22]

The role of impaired airway control in post-operative sleep disruption, and the contribution of opioids to this impairment, is not clear. In patients with sleep disordered breathing, repetitive episodes of airway narrowing or obstruction can cause severe loss of sleep.[23] Our patients showed more airway obstruction during wakefulness, than when sleeping. Airway obstruction can cause rapid arousal,[24 25] and it is possible that airway obstruction within a few moments of sleep onset was acting to rouse these patients. We classified an epoch when either obstruction or phasic abdominal activity was present, if there was any evidence of these features in the epoch. However, we only classified a 30-s epoch of recording as 'sleep' if more than half of this period was sleep pattern. This is a standard definition[6] and periods of sleep shorter than this would be considered the waking state. It is possible that airway obstruction at sleep onset could lead to arousal, allowing an apparent association between airway obstruction and wakefulness. This would also explain why there was less airway obstruction in the sleeping patients: those patients who were able to sleep would be those patients with less difficulty breathing. To confirm this possibility it would be necessary to assess these features at the same time, to observe the exact time relationships within the epoch. We could not do this and at the same time make an unbiased assessment of the relationships between the features being studied, but are conducting further studies to address this question. Catley and colleagues analysed their data in epochs of 5 min, so the relationship between sleep and abnormal breathing movements in their study may have been very different.[1]

Abdominal muscle activation is prominent in patients receiving opioids for analgesia after surgery.[2] Factors that may cause this activation include hypercapnia, partial airway obstruction,[26] and increased respiratory drive.[27 28] During sleep, respiratory drive is less, and this decrease in drive, and the reduced response to positive airway pressure,[29] may result in less frequent phasic activity during sleep. In animals, however, abdominal muscles are more active during slow wave sleep.[30 31] In the present study, the more frequent airway obstruction in the waking state could explain why phasic abdominal activity was likely during wakefulness. This increase in activity may aid ventilation, but at the expense of potentially reducing lung volume. This will impair gas exchange and reduce pulmonary oxygen stores making desaturation more rapid in the event of obstructive apnoea.[32] Episodic obstruction[33] and hypoxia[34] can cause hypertension and tachycardia, by a range of possible neural and humoral mechanisms, which may be harmful in patients after surgery.

Our findings suggest that airway obstruction can cause sleep disturbance and augment abdominal muscle activity. Satisfactory methods that can reduce these features after surgery remain to be defined, but could include non-opioid analgesics that have less influence on airway control than morphine.

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References

1 Catley DM, Thornton C, Jordan C, *et al.* Pronounced episodic oxygen desaturation in the post-operative period: its association

with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–8

2 Duggan J, Drummond GB. Activity of lower intercostal and abdominal muscle after upper abdominal surgery. *Anesth Analges* 1987; **66**: 852–5

3 Nimmo AF, Drummond GB. Respiratory mechanics after abdominal surgery measured with continuous analysis of pressure, flow and volume signals. *Br J Anaesth* 1996; **77**: 317–26

4 Duggan JE, Drummond GB. Abdominal muscle activity and intraabdominal pressure after upper abdominal surgery. *Anesth Analges* 1989; **69**: 598–603

5 Freund F, Roos A, Dodd RB. Expiratory activity of the abdominal muscles in man during general anesthesia. *J Appl Physiol* 1964; **19**: 693–7

6 Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring systems for sleep stages of human subjects. Bethesda, MD: US Government Printing Office, 1968

7 Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. *Sleep* 1997; **20**: 1175–81

8 Hosselet J-J, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. *Am J Resp Crit Care Med* 1998; **157**: 1461–7

9 Tjur T. Nonlinear regression, quasi likelihood, and overdispersion in generalized linear models. *Am Statistician* 1998; **52**: 222–7

10 Guyatt AR, Parker SP, McBride MJ. Measurement of human nasal ventilation using an oxygen cannula as a pilot-tube. *Am Rev Respir Dis* 1982; **126**: 434–8

11 Drummond GB, Nimmo AF, Elton RA. Thoracic impedance used for measuring chest wall movement in postoperative patients. *Br J Anaesth* 1996; **77**: 327–32

12 Ballester E, Badia JR, Hernandez L, *et al.* Nasal prongs in the detection of sleep-related disordered breathing in the sleep apnoea/hypopnoea syndrome. *Eur Respir J* 1998; **11**: 880–3

13 Series F, Marc I. Nasal pressure recording in the diagnosis of sleep apnoea hypopnoea syndrome. *Thorax* 1999; **54**: 506–10

14 Aurell J, Elmquist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *BMJ* 1985; **290**: 1029–32

15 Edwards GB, Schuring LM. Pilot study: validating staff nurses' observations of sleep and wake states among critically ill patients, using polysomnography. *Am J Crit Care* 2000; **2**: 125–31

16 DeTroyer A, Estenne M, Ninane V, VanGansbeke D, Gorini M. Transversus abdominis muscle function in humans. *J Appl Physiol* 1990; **68**: 1010–6

17 Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996; **76**: 552–9

18 Kay DC, Eisenstein RB, Jasinski DR. Morphine effects on human REM state, waking state and NREM sleep. *Psychopharmacology* 1969; **14**: 404–10

19 Keifer JC, Baghdoyan HA, Lydic R. Sleep disruption and increased apneas after pontine microinjection of morphine. *Anesthesiology* 1992; **77**: 973–82

20 Cronin A, Keifer JC, Baghdoyan HA, Lydic R. Opioid inhibition of rapid eye movement sleep by a specific mu receptor agonist. *Br J Anaesth* 1995; **74**: 188–92

21 Jones JG, Sapsford DJ, Wheatley RG. Postoperative hypoxemia—mechanisms and time course. *Anaesthesia* 1990; **45**: 566–73

22 Stone JG, Cozine KA, Wald A. Nocturnal oxygenation during patient-controlled analgesia. *Anesth Analges* 1999; **89**: 104–10

23 Hanning CD. Obstructive sleep apnoea. *Br J Anaesth* 1989; **63**: 477–88

24 Kay A, Trinder J, Bowes G, Kim Y. Changes in airway-resistance during sleep onset. *J Appl Physiol* 1994; **76**: 1600–7

25 Kay A, Trinder J, Kim Y. Individual differences in the relationship between upper airway resistance and ventilation during sleep onset. *J Appl Physiol* 1995; **79**: 411–9

26 Badr MS, Skatrud JB, Dempsey JA. Effect of chemoreceptor stimulation and inhibition on total pulmonary resistance in humans during nrem sleep. *J Appl Physiol* 1994; **76**: 1682–92

27 Ledlie JF, Kelsen SG, Cherniack NS, Fishman AP. Effects of hypercapnia and hypoxia on phrenic nerve activity and respiratory timing. *J Appl Physiol* 1981; **51**: 732–8

28 Takasaki Y, Orr D, Popkin J, Xie A, Bradley TD. Effect of hypercapnia and hypoxia on respiratory muscle activation in humans. *J Appl Physiol* 1989; **67**: 1776–84

29 Wakai Y, Welsh MM, Leevers AM, Road JD. Expiratory muscle activity in the awake and sleeping human during lung inflation and hypercapnia. *J Appl Physiol* 1992; **72**: 881–7

30 Dick TE, Parmeggiani PL, Orem J. Intercostal muscle activation during sleep in the cat: an augmentation of expiratory activity. *Respir Physiol* 1982; **50**: 255–65

31 Plowman L, Lauff DC, Berthon-Jones M, Sullivan CE. Abdominal muscle-activity in conscious dogs—effect of sleep and route of breathing. *Respir Physiol* 1990; **81**: 321–36

32 Fletcher EC, Costarangos C, Miller T. The rate of fall of arterial oxyhemoglobin saturation in obstructive sleep-apnea. *Chest* 1989; **96**: 717–22

33 Phillips BG, Somers VK. Neural and humoral mechanisms mediating cardiovascular responses to obstructive sleep apnea. *Respir Physiol* 2000; **119**: 181–7

34 Fletcher EC. Effect of episodic hypoxia on sympathetic activity and blood pressure. *Respir Physiol* 2000; **119**: 189–97

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Pulmonary scintigraphy for diagnosis of aspiration during intravenous propofol anaesthesia for colonoscopy[†]

S. Rezaiguia-Delclaux[1]*, B. Streich[1], D. Bouleau[1], J.-C. Delchier[2], G. Dhonneur[1], M. Meignan[3] and P. Duvaldestin[1]

[1]Department of Anaesthesiology, [2]Department of Gastroenterology and [3]Department of Nuclear Medicine, Hôpital Henri Mondor, AP-HP, Université Paris XII, 51 avenue du Maréchal de Lattre de Tassigny, F-94010 Créteil, France

**Corresponding author*

A specific technique for detection of pulmonary aspiration during the perioperative period is lacking. In this study, we developed a scintigraphic method for its diagnosis. Technetium 99m sulphur colloid was given orally 2 h before an i.v. infusion of propofol in patients undergoing elective colonoscopy. During the procedure, patients were spontaneously breathing 100% oxygen via a face mask. After recovery from anaesthesia, patients had a chest scinti-scan. As a control group, 10 healthy men were studied. The lung scan was considered positive if any tracer activity greater than background level was detected in the lung field. Among 96 patients studied, three patients had a positive chest scinti-scan. One of the three patients developed pneumonia while the other two remained asymptomatic. In none of the control asymptomatic group was tracer detected in the chest. We suggest that this technique is specific and can be used as a tool to assess the risk of pulmonary aspiration during different anaesthetic procedures.

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Keywords: lung, pulmonary aspiration; surgery, colonoscopy; anaesthetics i.v., propofol; measurement techniques, scintigraphy

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A specific method for detection of pulmonary aspiration during the perioperative period is lacking. The methods used previously during sedation or general anaesthesia have focused on regurgitation of gastric contents.[1 2] Interestingly, direct assessment of silent pulmonary aspiration has been described in unsedated patients with gastro-oesophageal reflux[3] using a simple and specific scintigraphic method.

Colonoscopy is a routine day-case procedure commonly carried out under i.v. sedation. In France, the 800 000 procedures performed each year account for 10% of all anaesthetics.[4] Various sedative regimen, including neuroleptics and benzodiazepines, may cause the loss of protective airway reflexes[5–7] and therefore potentially induce pulmonary aspiration of gastric contents. Patients undergoing colonoscopy often complain of gastrointestinal disorders or have other medical conditions associated with swallowing dysfunction, a large gastric fluid volume, or regurgitation. Moreover, increased intra-abdominal pressure as a result of colonic air insufflation, external abdominal compression or a change of body position are widely used to facilitate progression of the endoscope,[8] and may favour gastric regurgitation.

This study aimed to assess silent pulmonary aspiration by a specific scintigraphic method in patients undergoing elective colonoscopy under i.v. propofol.

Methods

Study population

Patients due to receive i.v. propofol infusion for elective colonoscopy were enrolled into the study. Pulmonary aspiration was evaluated prospectively by lung scinti-scan after institutional approval and informed written consent. Exclusion criteria were: age under 18 yr; conditions that predispose to pulmonary aspiration such as gastrointestinal obstruction, a pre-existing nasogastric tube, or a depressed level of consciousness; a swallowing disorder; or upper digestive endoscopy to be performed during the same procedure. The absence or presence of concomitant disease

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and its severity was rated using the ASA physical status classification.

Procedure

Patients were not pre-medicated. Two hours before the administration of propofol, patients swallowed in the upright position 0.5 mCi of technetium 99m sulphur colloid mixed in 10 ml of water, as a radioactive tracer. During the procedure, patients were placed in the supine position and turned to left lateral if necessary. Propofol 1.0–1.5 mg kg^{-1} was given as an i.v. bolus followed by a continuous infusion of 3 mg kg^{-1} h^{-1}. The infusion of propofol was switched off after forward movement of the colonoscope. All patients received supplemental oxygen via a face mask, started at least 5 min before the propofol infusion. The level of unconsciousness was defined as a loss of response to verbal commands. The heart rate was monitored continuously and the arterial pressure at 3 min intervals. Pulse oximetry and end-tidal carbon dioxide were recorded continuously during the procedure (Viridia, Hewlett-Packard) and pharyngeal obstruction was avoided by insertion of a Guedel airway when necessary. Patients were monitored in a recovery room for a minimum of 1 h after completion of the procedure. Perioperative side effects such as cough or decrease in oxygen saturation (Sp_{O_2}) below 90% for more than 30 s were noted for each patient.

The control group consisted of 10 healthy men aged 25–45 yr. None had any health problems or took any medication. All were asked to refrain from food and water for 12 h before the start of the study. After ingestion of the labelled suspension in the upright position, they remained supine for 2 h.

Diagnosis of pulmonary aspiration

As technetium 99m has a half-life of 6 h, patient and control scans were performed 3–6 h after administration of the radiotracer. Once patients had fully recovered consciousness, they were transferred to the nuclear medicine department for lung scanning (anterior and posterior view) using a Gamma camera (Elscint). Scans were interpreted independently by a nuclear medicine physician. Scan results were considered positive when the tracer was detected within the thorax and lateral to the midline. A scan that showed the tracer only in the midline of the thorax was considered negative, because this localization could correspond to the oesophagus. A scan was also considered negative if it showed tracer in the pharynx or the stomach. A chest x-ray was performed in each patient with a positive scinti-scan.

Statistical analysis

Age, weight, and duration of colonoscopy were expressed as mean (SD), and categorical variables (sex ratio, ASA physical status) as percentage.

Results

During the given time period, 96 patients completed the study (mean age 55 (15) yr; mean weight 70 (12) kg; male 63%; ASA I: 32%; II: 50%; III: 18%). The mean duration of colonoscopy was 24 (13) min. In order to facilitate

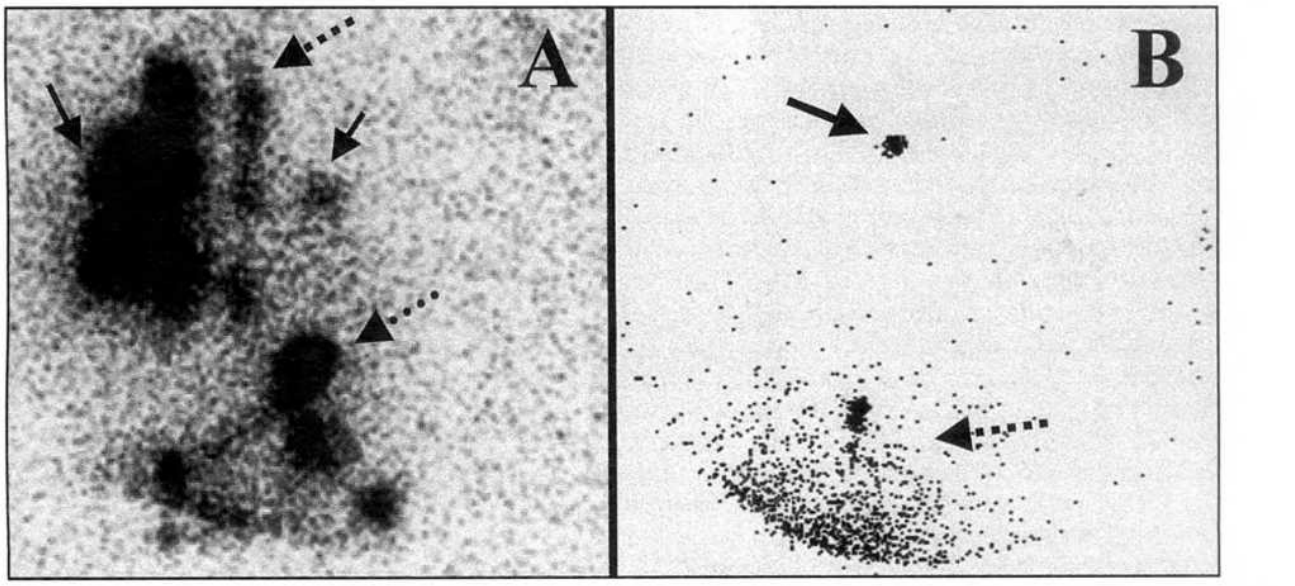

Fig 1 (A) Example of a positive scintigraph. Anterior view of the chest: the tracer was detected within the thorax and lateral to the midline (lung localization: solid arrow). The localization within the thorax in the midline could represent either trachea or oesophagus (dashed arrow). (B) Example of a negative scintigraph. Anterior view of the chest: the radiotracer was only detected in the pharynx (solid arrow) and in the stomach area (dashed arrow).

progression of the endoscope, external abdominal compression was used in all the patients and body position was changed (from supine to left lateral) in 30%. Perioperative symptoms such as cough or decreased Sp_{O_2} occurred in 10 out of 96 patients (cough, 10; decreased Sp_{O_2}, 5). Three cases of pulmonary aspiration defined by a positive scintiscan were diagnosed (Fig. 1A). Of these three patients, two coughed during the procedure. One of these patients developed transient hypoxaemia and bilateral pulmonary infiltrates on the chest x-ray, which resolved after one week of antibiotic treatment. The postoperative course of the other two patients with a positive scinti-scan was uneventful; the control chest x-ray revealed no abnormalities. In none of the healthy control group was tracer detected in the chest (Fig. 1B).

Discussion

In this study, pulmonary aspiration of gastric contents was assessed directly using a simple scintigraphic method, enabling diagnosis of silent aspiration in patients who underwent elective colonoscopy under propofol infusion.

Several techniques have been developed in the past to assess the incidence of pulmonary aspiration or regurgitation of gastric contents, such as examination of pharyngeal or tracheal aspirates for acidity[1] or ingested dyes.[2] Dye indicators such as methylene blue,[2] contained in a capsule, were swallowed before induction of anaesthesia and their presence in the pharynx or the trachea was assessed at the end of the surgery, before recovery from anaesthesia. As half of all pulmonary aspirations occur in the early postoperative period,[9] the incidence of pulmonary aspiration may be underestimated by this approach. In the current study, patients swallowed technetium 99m sulphur colloid before the propofol infusion and pulmonary aspiration was defined as detection of the labelled tracer in the pulmonary field. This method allowed us to study all the perioperative period until complete recovery from anaesthesia. This diagnostic approach has previously been used in awake patients with gastro-oesophageal reflux[3] and in intensive care patients undergoing controlled ventilation and treated with enteral nutrition.[10] Technetium 99m sulphur colloid is insoluble in water and not absorbed through mucous membranes or the gastrointestinal tract, so that any labelled tracer found in the lung parenchyma must have been aspirated.

The 3% incidence of pulmonary aspiration during i.v. propofol for elective colonoscopy found in this study may be considered high. Such pulmonary aspiration includes silent aspiration and thus comparison with other studies can be misleading. Studies based on examination of pharyngeal or tracheal aspirates for acidity or ingested dyes have also indicated a high incidence of regurgitation during anaesthesia (4–26%); detectable aspiration occurred in as many as 13–20% of cases.[11–14] In contrast, life-threatening pulmonary aspiration in the perioperative period is uncommon: the incidence derived from large anaesthesia surveys varies from 1 in 1560 to 1 in 7140 anaesthetics.[9 15 16]

In summary, a radioisotope scinti-scanning technique to diagnose pulmonary aspiration was used in 96 patients undergoing elective colonoscopy. We found the incidence of detectable pulmonary aspiration to be 3%, without serious morbidity.

References

1 Miller C, Anderson W. Silent regurgitation in day case gynaecological patients. *Anaesthesia* 1988; **43**: 321–3

2 Barker P, Langton J, Murphy P, Rowbotham D. Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway. *Br J Anaesth* 1992; **69**: 314–5

3 Chernow B. Pulmonary aspiration as a consequence of gastroesophageal reflux: a diagnostic approach. *Digest Dis Sci* 1979; **24**: 839–44

4 Clergue F, Auroy Y, Péquignot F, Jongla E, Lienhart A, Laxenazire M-C. French survey of anaesthesia in 1996. *Anesthesiology* 1999; **91**: 1509–20

5 Cotton B, Smith G. The lower oesophageal sphincter and anaesthesia. *Br J Anaesth* 1984; **56**: 37–46

6 Murphy P, Erskine R, Langton J. The effects of intravenously administered diazepam, midazolam and flumazenil on the sensitivity of upper airway reflexes. *Anaesthesia* 1994; **49**: 105–10

7 Rimaniol J, Dhonneur G, Duvaldestin P. Recovery of the swallowing reflex after propofol anaesthesia. *Anesth Analg* 1994; **79**: 856–9

8 Waye J, Yessayan S, Lewis B, Fabry T. The technique of abdominal pressure in total colonoscopy. *Gastrointest Endosc* 1991; **37**: 147–51

9 Warner M, Warner M, Weber J. Clinical signifiance of pulmonary aspiration during the perioperative period. *Anesthesiology* 1993; **78**: 56–62

10 Torres A, Serra-Battles J. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992; **116**: 540–3

11 Berson W, Adriani J. 'Silent' regurgitation and aspiration during anaesthesia. *Anesthesiology* 1954; **15**: 644–9

12 Blitt C, Gutman H, Cohen D, Weissman H, Dillon JB. 'Silent' regurgitation and aspiration during general anaesthesia. *Anesth Analg* 1970; **49**: 707–13

13 Carlsson C, Islander G. Silent gastropharyngeal regurgitation during anaesthesia. *Anesth Analg* 1981; **60**: 655–65

14 Turndorf H, Rodis I, Clark T. 'Silent' regurgitation during general anaesthesia. *Anesth Analg* 1974; **53**: 700–3

15 Mellin-Olson J, Fasting S, Gisvold S. Routine preoperative gastric emptying is seldom indicated. A study of 85 594 anaesthetics with special focus on aspiration pneumoniae. *Acta Anaesthesiol Scand* 1996; **40**: 1184–8

16 Olsson G, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185 358 anaesthetics. *Acta Anaesthesiol Scand* 1986; **30**: 84–92

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Manoeuvres used to clear the airway during fibreoptic intubation

V. K. Durga, J. P. Millns and J. E. Smith*

Department of Anaesthesia, University Hospital Birmingham, Selly Oak Hospital, Birmingham B29 6JD, UK
**Corresponding author*

Fibreoptic orotracheal endoscopy under general anaesthesia may be more difficult to perform if the upper airway cannot be fully cleared. We have studied the effectiveness of jaw thrust, lingual traction and the application of both manoeuvres simultaneously, in opening up the orolaryngeal airspace in 30 ASA group 1 or 2 patients aged between 16 and 70 yr undergoing elective general surgery requiring orotracheal intubation. Airway clearance was assessed fibreoptically at soft palate level by observing whether or not the uvula or soft palate was apposed to the base of the tongue, and at epiglottic level by observing whether or not the epiglottis was apposed to the posterior pharyngeal wall. Lingual traction with Duval's forceps cleared the tongue away from the uvula and soft palate significantly more times than did jaw thrust ($P<0.05$). Jaw thrust cleared the epiglottis away from the posterior pharyngeal wall more frequently than did lingual traction ($P=0.052$). Applying both jaw thrust and lingual traction simultaneously cleared the airway at both soft palate and epiglottic level in every patient. When used alone, jaw thrust and lingual traction fail to produce full airway clearance in a significant number of patients. Combined jaw thrust and lingual traction clears the airway more effectively but requires two assistants.

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Keywords: intubation tracheal, technique; equipment, fibreoptic laryngoscope

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Orotracheal and nasotracheal fibreoptic intubation can be performed in both awake and anaesthetized patients.[1] Awake patients usually maintain clear airways but in anaesthetized patients, muscle tone is reduced and the soft palate, base of tongue, and epiglottis all approximate to the posterior pharyngeal wall.[2–5] Partial or complete obstruction of the airway may make fibreoptic endoscopy more difficult and, therefore, techniques that open up the airway are required. In fibreoptic nasal intubation, head extension, chin lift, and jaw thrust can be fully applied, but in fibreoptic oral intubation, although head extension is possible, the chin lift manoeuvre cannot be fully applied because the mouth must be kept open. The three main ways of resolving this problem are: to use intubating airways;[1 6–11] to apply jaw thrust with the mouth open;[1 12–15] or to apply lingual traction.[1 16–19] Intubating airways, such as the Berman[6] or Ovassapian[7] airways, are often very useful as they not only clear the airway but also tend to direct the fibrescope tip towards the vocal cords. When using these devices, however, it has been shown that sometimes multiple manipulations are required and that endoscopy and intubation may be prolonged or may fail.[19–22] Alternative fibreoptic techniques may, therefore, be required. Orotracheal fibreoptic intubation without the use of intubating airways may be facilitated either by jaw thrust with the mouth open or by lingual traction, at the discretion of the endoscopist. There have been no controlled trials comparing the relative effectiveness of these two manoeuvres in opening up the orolaryngeal airspace in anaesthetized patients. It would be useful to know which method is most effective, if any, as this information might enable anaesthetists to perform fibreoptic endoscopy and intubation more swiftly and reliably. This study, therefore, aimed to compare and contrast airway clearance produced by jaw thrust (with the mouth open), with lingual traction, and with both manoeuvres applied simultaneously.

Methods

The investigation was approved by the South Birmingham Local Research Ethics Committee and informed, written consent was obtained from each patient. Thirty ASA class 1 or 2 patients aged between 16 and 70 yr undergoing elective general surgery that required orotracheal intubation as part of their anaesthetic management were studied. Patients with morbid obesity (Body Mass Index >35), oesophageal reflux, or known or suspected difficult intubation were excluded from the study.

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Each patient's airway was assessed preoperatively and the Mallampati score and thyromental distance were recorded. Electrocardiogram, indirect arterial pressure, arterial oxygen saturation, and carbon dioxide concentrations were monitored. Glycopyrrolate 200–400 µg was administered i.v. and the patient was given 100% oxygen. Anaesthesia was induced with fentanyl 1 µg kg^{-1} and propofol 2.5 mg kg^{-1} followed by atracurium 0.5 mg kg^{-1} and the patient's lungs were ventilated with isoflurane in oxygen, using a face mask attached to a circle system, until muscle relaxation was complete.

Upper airway endoscopies were performed using an Olympus LF2 fibreoptic laryngoscope attached to an endoscopic video camera system and a videotape recorder. Videotape recordings of the endoscopies were made following General Medical Council guidelines. The investigation team comprised an anaesthetist experienced in fibreoptic endoscopy (VKD or JPM) and two assistants. The first assistant, another anaesthetist (JES), stood on the patient's right-hand side and the second assistant, a trained operating department assistant, stood on the patient's left-hand side. The assistants were blinded from the television screen and were unaware of the findings during the endoscopy. Three airway manoeuvres were carried out on each patient and all the patients acted as their own control.

The patient's head rested on a single pillow and the atlanto-occipital joint was extended. The first assistant applied firm jaw thrust, keeping the patient's mouth open, and the operator then advanced the fibrescope, onto which had been threaded a tracheal tube, into the mouth along the dorsum of the tongue. Airway clearance at the level of the soft palate was assessed by observing whether or not the uvula, or uvula and soft palate, were in contact with the dorsum of the tongue. The fibrescope was then advanced into the oropharynx and airway clearance at epiglottic level was assessed by observing whether or not the epiglottis was in contact with the posterior pharyngeal wall. If the uvula, or the uvula and base of uvula, touched the tongue or if the sides of the epiglottis touched the posterior pharyngeal wall, the airway was classified as partially obstructed at the respective levels. If the whole of the soft palate was in contact with the tongue or if the sides and tip of the epiglottis were in contact with the posterior pharyngeal wall, the airway was classified as completely obstructed at the respective levels. If these structures were not in contact, the airway was classified as clear at the respective levels.

The fibrescope was then removed and the first assistant applied a large-sized Duval's lung forceps to the tongue and carefully lifted the tongue anteriorly until minimal resistance was felt. Lingual traction was applied in the vertical plane so that the lower incisors did not make contact with the ventral surface of the tongue. The forceps were then held in the second assistant's left hand while his right hand maintained extension of the atlanto-occipital joint. The fibrescope was advanced into the mouth and oropharynx and airway clearance at soft palate and epiglottic level was assessed as before.

Table 1 Patient characteristics (mean (range or SD) or number)

No.	Age (yr)	Weight (kg)	Sex (M/F)	Scheduled surgery
30	47.6 (21–70)	77.6 (13.7)	18/12	Laparoscopic surgery 7 Ano-rectal surgery 7 Unilateral thyroid lobectomy 6 Hemicolectomy 4 Others 6

The fibrescope was removed from the mouth again and the first assistant applied jaw thrust, keeping the mouth open, in addition to the lingual traction. The fibrescope was again advanced into the mouth and oropharynx and airway clearance was assessed as described. The fibrescope was advanced through the vocal cords, into the trachea and down to the carina. The Duval's forceps were removed and the tracheal tube was passed over the fibrescope into the trachea to complete the intubation. The dorsal and ventral surfaces of the tongue were examined for any signs of injury. Anaesthesia and surgery then proceeded as usual. The videotape recording was later reviewed to validate the observations. A maximum time of 90 s was allowed for the investigation. If the observations could not be completed within this time limit, the patient was withdrawn from the trial and intubated immediately. All patients were visited next day and asked if they had a sore throat or sore tongue, and the tongue was again examined.

Airway clearance when using jaw thrust and lingual traction at soft palate and epiglottic level were compared using Fisher's exact test. The associations between airway clearance, when using both jaw thrust and lingual traction, and the patients' Mallampati scores were analysed using Fisher's exact test.

Results

Patient characteristics are shown in Table 1. After induction of anaesthesia, the lungs of all the patients were easy to ventilate with a face mask and anaesthetic system. All the endoscopic examinations were completed within the 90 s time limit and arterial oxygen saturation did not fall below 96% in any patient. All patients had thyromental distances greater than 6 cm. Twenty patients had Mallampati scores of 1, nine had Mallampati scores of 2 and one had a Mallampati score of 3. No other predictors of difficult intubation were found on airway examination.

Table 2 shows the number of clear and partially or fully obstructed airways at soft palate and epiglottic level. At soft palate level, with jaw thrust, the airways of six patients were obstructed. The uvula and base of uvula only were in apposition to the tongue in four of these patients and both uvula and soft palate were in apposition to the tongue in the other two patients. At soft palate level, with lingual traction,

Table 2 Number of clear and partially or fully obstructed airways at soft palate and epiglottic levels with jaw thrust, lingual traction and combined jaw thrust and lingual traction. *$P<0.05$ proportion of obstructions with jaw thrust compared with proportion of obstructions with lingual traction at soft palate level. †$P=0.052$ proportion of obstructions with lingual traction compared with proportion of obstructions with jaw thrust at epiglottic level

Airway	**Soft palate**			**Epiglottis**		
	Jaw thrust (JT)	**Lingual traction** (LT)	**Combined** JT and LT	**Jaw thrust** (JT)	**Lingual traction** (LT)	**Combined** JT and LT
Clear	24*	30*	30	29†	23†	30
Obstructed	6*	0*	0	1†	7†	0

Table 3 Airway clearance at soft palate and epiglottic level with jaw thrust in relation to Mallampati scores. 'Obstructed' includes both partial and complete obstruction. *$P<0.05$ proportion of obstructions with Mallampati 2 or 3 compared with proportion of obstructions with Mallampati 1 at soft palate level

Airway	**Soft palate**		**Epiglottis**	
	Mallampati 1	**Mallampati 2 or 3**	**Mallampati 1**	**Mallampati 2 or 3**
Clear	19*	5*	20	9
Obstructed	1*	5*	0	1

Table 4 Airway clearance at soft palate and epiglottic level with lingual traction in relation to Mallampati scores. 'Obstructed' includes both partial and complete obstruction

Airway	**Soft palate**		**Epiglottis**	
	Mallampati 1	**Mallampati 2 or 3**	**Mallampati 1**	**Mallampati 2 or 3**
Clear	20	10	16	7
Obstructed	0	0	4	3

Table 5 Airway clearance at soft palate level with jaw thrust and at epiglottic level with lingual traction in relation to the 15 heaviest patients (mean weight 87.9 kg) and the 15 lightest patients (mean weight 67.2 kg). 'Obstructed' includes both partial and complete obstruction

Airway	**Tongue clearance with jaw thrust**		**Epiglottis clearance with lingual traction**	
	15 heaviest patients	**15 lightest patients**	**15 heaviest patients**	**15 lightest patients**
Clear	13	11	10	13
Obstructed	2	4	5	2

neither the soft palate nor the uvula were in apposition to the tongue in any patient. At epiglottic level, the sides, but not the tip, of the epiglottis were in apposition to the posterior pharyngeal wall in one patient with jaw thrust, and in seven patients with lingual traction. Lingual traction with Duval's forceps cleared the tongue away from the soft palate significantly more times than did jaw thrust ($P<0.05$). Jaw thrust cleared the epiglottis away from the posterior pharyngeal wall more frequently than did lingual traction ($P=0.052$). Applying both jaw thrust and lingual traction as a combined manoeuvre cleared the airway at both soft palate and epiglottic level in every patient. The patient with the Mallampati score of 3 had both a fully obstructed airway at pharyngeal level with jaw thrust and also the sides of the epiglottis were apposed to the posterior pharyngeal wall with lingual traction. Again, the application of both manoeuvres completely cleared this patient's airway. All the other patients with positive signs of partial or complete airway obstruction had the obstruction present at only one level and with only one of the manoeuvres.

At soft palate level with jaw thrust, significantly more patients with Mallampati 2 or 3 scores had uvula or uvula and soft palate in apposition to the tongue than did patients with Mallampati 1 scores (five out of 10 as apposed to one out of 20) (Table 3). At epiglottic level with jaw thrust, however, Mallampati scores were not significantly related to airway obstruction (one out of 10 as apposed to zero out of 20) (Table 3). With lingual traction, Mallampati scores were not related to airway obstruction at soft palate level nor at epiglottic level (Table 4).

As obese patients may be expected to have more airway obstruction under anaesthesia than non-obese patients, the 15 heaviest patients (mean weight 87.9 kg) were compared with the 15 lightest patients (mean weight 67.2 kg) with respect to obstruction with jaw thrust and with lingual traction (Table 5). Although lingual traction appeared to be less effective in fully clearing the epiglottis in heavier patients, the results did not achieve statistical significance in this sample ($P=0.39$). There was no statistically significant difference between the number of obstructions observed in males and females.

Fourteen (47%) of the patients had sore throats on the first post-operative day. In 11 patients, the sore throat was described as mild and in three patients as moderate. No patient complained of sore tongue. There were no symptoms or signs of injury to the tongue in any of the patients either immediately after intubation nor on the first post-operative day.

Discussion

Orotracheal fibreoptic intubation, both with[1 6–11] and without[1 12–19] intubating airways, is a widely practised and widely taught technique. This study aimed to identify problems that might occur when the procedure is carried out without using intubating airways and also attempted to investigate ways of alleviating these problems. The study shows that although jaw thrust with the mouth open is a very effective way of clearing the epiglottis away from the posterior pharyngeal wall, it is less successful in clearing the tongue away from the soft palate. Contrastingly, although lingual traction with Duval's forceps is a very effective way of clearing the tongue away from the soft palate, it is less successful at fully clearing the epiglottis away from the posterior pharyngeal wall. Hence, when used alone, both manoeuvres fail to produce full airway clearance in a significant number of patients undergoing fibreoptic endoscopy under general anaesthesia. When both jaw thrust and lingual traction were applied simultaneously, however, all airways were fully cleared at both levels. These observations had clear endpoints and as all three manoeuvres were tested in each patient, the patients acted as their own controls. In this investigation, we studied patients with normal airways who were not expected to present with a difficult intubation. It is possible that the manoeuvres may be less successful in patients with a difficult intubation, but at present there are no data to confirm this.

As fibreoptic endoscopy relies on clear airspace ahead of the fibrescope tip, increasing airway obstruction may cause increasing difficulty. At pharyngeal level, apposition of the uvula base to the tongue did not usually cause undue difficulty as the fibrescope could be passed to one side of it. However, in the two patients with both uvula and soft palate apposed to the tongue, it was difficult to obtain a view of the larynx and several 'blind' attempts had to be made before the epiglottis was seen. At epiglottic level, when the sides of the epiglottis only were apposed to the posterior pharyngeal wall, with careful manipulations, it proved possible to pass the fibrescope beneath the tip of the epiglottis in all patients. No patient in our series had the tip of the epiglottis apposed to the posterior pharyngeal wall, but our previous experience suggests that when this circumstance does arise, endoscopy is particularly difficult.

Our figures also demonstrated that with jaw thrust, patients with Mallampati 2 or 3 scores had more incidents of obstruction at soft palate level than patients with Mallampati 1 scores. Also, the only patient with a Mallampati 3 score in our series had obstruction with both jaw thrust and lingual traction at both airway levels. Hence, potentially difficult conventional direct laryngoscopy may be associated with difficult fibreoptic laryngoscopy. When both manoeuvres were applied simultaneously, however, the airway was fully cleared. It would be useful to know whether the combined manoeuvre works as well in patients with possible or confirmed difficult laryngoscopy. Further work would be required to investigate this possibility. The combined technique is particularly helpful in fibreoptic training as inexperienced personnel have greater difficulty in performing endoscopy when airway clearance is less than perfect.

During general anaesthesia, posterior displacements of the tongue, soft palate, and epiglottis tend to close the airway.[2–5] The primary manoeuvres used to clear the airway comprise chin lift, extension of the atlanto-occipital joint and anterior displacement of the mandible. These manoeuvres may be further refined by allowing the lips and teeth to separate slightly (triple airway manoeuvre)[3 23] so that exhalation is not impeded. Considerably more mouth opening is needed during fibreoptic instrumentation and this may partly explain why partial or complete airway obstruction was seen in some of our patients. It is recognized that the mouth open position may compromise airway patency.[3 24]

When electing to perform oral fibreoptic intubation without intubating airways, or if satisfactory airway clearance cannot be secured when an intubating airway is being used, perhaps the first manoeuvre to try is jaw thrust with the mouth open, as this is the simplest and least invasive approach. If this does not help because of apposition of the tongue and soft palate, then lingual traction might be applied by a trained assistant as there is a good chance that this manoeuvre will successfully treat this type of airway obstruction. A better alternative, if a second anaesthetist is present and familiar with the techniques, is to apply both manoeuvres simultaneously. The efficacy of the combined manoeuvre is one of the reasons why a known or suspected difficult intubation being managed under general anaesthesia should involve two anaesthetists. At present, it is not known whether using intubating airways or applying jaw thrust and lingual traction simultaneously is the more reliable way of clearing the airway in fibreoptic orotracheal intubation of patients known to be a difficult intubation.

References

1 Ovassapian A. *Fiberoptic Endoscopy and the Difficult Airway*, 2nd edn. Philadelphia, PA: Lippincott–Raven, 1996; 71–103
2 Safar P, Escarraga LA, Chang F. Upper airway obstruction in the unconscious patient. *J Appl Physiol* 1959; **14**: 760–4
3 Morikawa S, Safar P, DeCarlo J. Influence of the head-jaw position upon upper airway patency. *Anesthesiology* 1961; **22**: 265–70
4 Boidin MP. Airway patency in the unconscious patient. *Br J Anaesth* 1985; **57**: 306–10
5 Nandi PR, Charlesworth CH, Taylor SJ, Nunn JF, Dore CJ. Effect of general anaesthesia on the pharynx. *Br J Anaesth* 1991; **66**: 157–62
6 Berman RA. A method for blind intubation of the trachea or oesophagus. *Anesth Analg* 1977; **56**: 866–7
7 Ovassapian A. A new fiberoptic intubating airway. *Anesth Analg* 1987 (Suppl); **66**: S132
8 Ovassapian A, Yelich SJ. Learning fiberoptic intubation. *Anesthesiology Clin N Am* 1991; **9**: 175–85

9 Mason RA. Learning fibreoptic intubation: fundamental problems. *Anaesthesia* 1992; **47**: 729–31

10 Morris IR. Continuing medical education: fibreoptic intubation. *Can J Anaesth* 1994; **41**: 996–1008

11 Erb T, Hampl KF, Schurch M, Kern CG, Marsch SCU. Teaching the use of fiberoptic intubation in anesthetized spontaneously breathing patients. *Anesth Analg* 1999; **89**: 1292–5

12 Roberts JT. Preparing to use the flexible fiber-optic laryngoscope. *J Clin Anesth* 1991; **3**: 64–75

13 Schaefer HG, Marsch SCU. Comparison of orthodox with fibreoptic orotracheal intubation under total I.V. anaesthesia. *Br J Anaesth* 1991; **66**: 608–10

14 Hartley M, Morris S, Vaughan RS. Teaching fibreoptic intubation. Effect of alfentanil on the haemodynamic response. *Anaesthesia* 1994; **49**: 335–7

15 Lucas DN, Yentis SM. A comparison of the intubating laryngeal mask tracheal tube with a standard tracheal tube for fibreoptic intubation. *Anaesthesia* 2000; **55**: 358–61

16 Witton TH. An introduction to the fiberoptic laryngoscope. *Can J Anaesth* 1981; **28**: 475–80

17 Smith JE, Mackenzie AA, Scott-Knight VCE. Comparison of two methods of fibrescope-guided tracheal intubation. *Br J Anaesth* 1991; **66**: 546–50

18 Cole AFD, Mallon JS, Rolbin SH, Ananthanarayan C. Fiberoptic intubation using anesthetized, paralyzed, apneic patients: Results of a residency training program. *Anesthesiology* 1996; **84**: 1101–6

19 Hakala P, Randell T, Valli H. Laryngoscopy and fibreoptic intubation in acromegalic patients. *Br J Anaesth* 1998; **80**: 345–7

20 Hakala P, Randell T. Comparison between two fibrescopes with different diameter insertion cords for fibreoptic intubation. *Anaesthesia* 1995; **50**: 735–7

21 Randell, Valli H, Hakal P. Comparison between the Ovassapian intubating airway and the Berman intubation airway in fibreoptic intubation. *Eur J Anaesth* 1997; **14**: 380–4

22 Aoyama K, Seto A, Takenaka I. Simple modification of the Ovassapian fiberoptic intubating airway. *Anesthesiology* 1999; **91**: 897

23 Benumof JL. Nonintubation management of the airway: mask ventilation. In: Benumof JL, ed. *Airway Management: Principles and Practice.* St Louis: Mosby, 1996; 233

24 Meurice JC, Marc I, Carrier G, Series F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. *Am J Respir Crit Care Med* 1996; **153**: 255–9

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A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients[†]

J. R. C. Jansen[1]*, J. J. Schreuder[2], J. P. Mulier[3], N. T. Smith[4], J. J. Settels[5] and K. H. Wesseling[5]

[1]Department of Intensive Care, Leiden University Medical Centre, The Netherlands. [2]Department of Cardiac Surgery, San Raffaele Hospital, Milan, Italy and CARIM, University of Maastricht, The Netherlands. [3]Department of Anaesthesiology, University of Leuven, Belgium. [4]Department of Anaesthesiology, University of California San Diego, CA, USA. [5]TNO Biomedical Instrumentation, Academic Medical Centre, Amsterdam

**Corresponding author*

In three clinical centres, we compared a new method for measuring cardiac output with conventional thermodilution. The new method computes beat-to-beat cardiac output from radial artery pressure by simulating a three-element model of aortic input impedance, and includes non-linear aortic mechanical properties and a self-adapting systemic vascular resistance. We compared cardiac output by continuous model simulation (MF) with thermodilution cardiac output (TD) in 54 patients (18 female, 36 male) undergoing coronary artery bypass surgery. We made three or four conventional thermodilution estimates spread equally over the ventilatory cycle. In 490 series of measurements, thermodilution cardiac output ranged from 2.1 to 9.3, mean 5.0 litre min^{-1}. MF differed +0.32 (1.0) litre min^{-1} on average with limits of agreement of −1.68 and +2.32 litre min^{-1}. Differences decreased when the first series of measurements in a patient was used to calibrate the model. In 436 remaining series, the mean difference became −0.13 (0.47) litre min^{-1} with limits of agreement of −1.05 and +0.79 litre min^{-1}. When consecutive measurements were made, the change was greater than 0.5 litre min^{-1}, on 204 occasions. The direction of change was the same with both methods in 199. The difference between the methods remained near zero during surgery suggesting that a single calibration per patient was adequate. Aortic model simulation with radial artery pressure as input reliably monitors changes in cardiac output in cardiac surgery patients. Before calibration, the model cannot replace thermodilution, but after calibration the model method can quantitatively replace further thermodilution estimates.

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Clinically, cardiac output is usually estimated intermittently with the thermodilution method. However, a continuous estimate of cardiac output in haemodynamically unstable patients, such as those undergoing cardiac or vascular surgery, would be preferable as continuous monitoring of cardiac output may provide an early warning of changes in circulatory function.

Many methods have been proposed to do this, including arterial pulse contour analysis;[1–3] transoesophageal,[4] transtracheal,[5] and intrapulmonary artery Doppler;[6] the Fick principle;[7] continuous thermodilution;[8–11] and bioimpedance.[12 13] To gain widespread acceptance, however, obstacles must be removed such as physiological limitations, limited reliability, cumbersome maintenance, insufficient precision, and slow responsive have to be overcome.

The 'Modelflow' method maybe suitable.[14–17] This method derives an aortic flow waveform from arterial pressure by simulation of a non-linear three-element aortic input impedance model and integrates stroke volume from

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the flow waveform. The method is now fully automatic, self-recording and has a fast response, and its precision appears substantially improved compared with earlier methods.[2] We studied bias, precision and tracking ability in 54 cardiac surgery patients, in three hospitals, by simultaneous comparison with right heart thermodilution estimates of cardiac output.

Materials and methods

Patients

The departments of Anesthesiology of the Veterans Administration Medical Center, San Diego, CA, USA (San Diego), the University of Leuven Academic Hospital, Leuven, Belgium (Leuven), and the University of Maastricht Academic Hospital, Maastricht, The Netherlands (Maastricht) participated in a prospective study of the bias and precision of the continuous cardiac output method compared with thermodilution, under conditions of routine use during cardiothoracic surgery. With approval of each institution's ethical committee and written informed consent from the patient, we studied 54 patients (18 female, 36 male), undergoing elective coronary artery bypass surgery. All patients had symptomatic coronary artery disease without previous myocardial infarction. We excluded patients with a history of abnormal ventricular function, known tricuspid or pulmonary valve disease, aortic valve abnormality, or aortic aneurysm. None had acute or chronic pulmonary disease.

The anaesthesia regimen differed slightly between the three hospitals. Premedication was with lorazepam (Maastricht, Leuven) or midazolam (San Diego). Anaesthesia was induced with sufentanil and maintained by further continuous infusion of sufentanil (Maastricht), or by injections of midazolam and fentanyl (San Diego), or of etomidate and sufentanil (Leuven) as needed. Complete muscle relaxation was maintained with pancuronium bromide (Maastricht), pipecuronium (San Diego), or vecuronium (Leuven). Patients were ventilated without PEEP, at a rate of approximately 10 bpm. Ventilatory volume and/or frequency were adjusted to maintain between 32 and 42 mm Hg. To control arterial pressure after sternotomy, in some cases during dissection of the internal mammary artery, and after bypass, nitroglycerine or nitroprusside were given. Some of the patients received phenylephrine, dopamine, or dobutamine.

Study plan

Cardiac output was measured continuously from the arterial pressure and thermodilution series were performed at times when identifiable changes in a patient's state occurred. Principally, a few minutes after the induction of anaesthesia, immediately after sternotomy, just before and after bypass, after sternal closure, after changes in drug infusion rate, after cardiac pacemaker rate changes, and after the completion of surgery. No measurements were made during bypass because of the absence of arterial pulsations. The number of measurements made in each patient depended on the duration of surgery and on the complexity of the surgical procedure. The series after induction of anaesthesia, however, was always obtained. Measurements were called and executed by an operator after permission from the anesthetist in charge and a statement of *no objection* from the surgeon. After pressing the start button, the cold liquid injections for the thermodilution estimates and the recording of all data was fully automatic by computer without human intervention thereby removing any operator bias or error. To improve haemodynamic stability, major surgery was suspended during the measurements.

Modelflow method physiologic background

Left ventricular contraction causes inflow of blood into the arterial system, but this inflow is opposed by arterial counter pressure and aortic and peripheral arterial input impedance. The Modelflow method simulates this behaviour. A haemodynamic model of arterial input impedance is used which is known to have realistic properties in computing stroke volume: the extended Windkessel model (Fig. 1).[18 19] The model has three principal components: a characteristic impedance which represents the opposition of the aorta to pulsatile inflow, Windkessel compliance which represents the opposition of the aorta to volume increases, and peripheral resistance which represents the opposition of the vascular beds to blood flow. These components are not constant. Impedance and compliance depend on pressure itself,[20] and total systemic peripheral resistance depends on many factors including circulatory filling, metabolism, sympathetic tone, and vasoactive drugs.

Aortic compliance decreases substantially when pressure increases. This non-linear behaviour of the aorta would be a

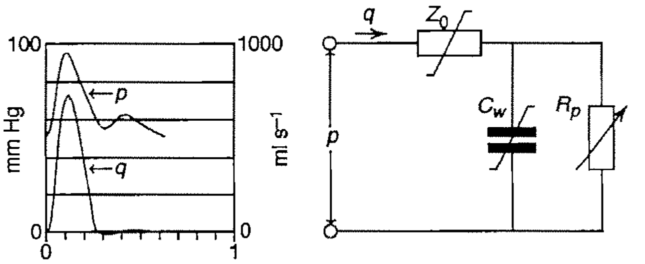


Fig 1 Schematic diagram of the three-element non-linear, self-adapting model (right) and input pressure and simulated flow pulse (left). Arterial pressure p is applied to the model input. Z_0, characteristic impedance of the proximal aorta; Cw, arterial Windkessel compliance; Rp, total systemic peripheral resistance. The non-linear properties of Z_0 and Cw are indicated by a stylized 'S' symbol. Rp has an arrow indicating that it adapts to changes in systemic resistance. The result of the model simulation is a flow curve q. Integrated per beat (the area under the curve) it yields stroke volume.

major source of error if not taken into account. In contrast, aortic characteristic impedance, increases only moderately with pressure. These non-linear relationships were studied *in vitro* by Langewouters and colleagues[20] and described as mathematical functions whose properties depend closely on patient age and gender, and slightly on height and weight. However, the aortic diameter is not known accurately. So, the absolute value of the computed cardiac output is uncertain unless calibration against another method of measurement such as thermodilution can be done. Theoretically, the thoracic aortic diameter could be measured for example with ultrasound, but this possibility was not tested. The tracking of changes in cardiac output, however, is not affected by the uncertainty of aortic diameter.[14]

Use of the Modelflow method

Before the start of surgery the patient's gender, age, height, and weight are entered into the Modelflow computer. These determine pressure-volume, pressure-compliance, and pressure-characteristic impedance relationships using Langewouters' equations, which are population averages. Look-up tables are formed in computer memory for each pressure level from the equations. At each new pressure sample taken at 100 Hz the corresponding values are read from the table and entered into the model. The model is simulated digitally in real-time and supplied with the sampled arterial pressure waveform. The pressure waveform is taken from the monitor in use in the operating room. The simulation result is a sampled continuous aortic flow waveform (Fig. 1). The flow waveform is integrated during arterial systole to deliver stroke volume. Cardiac output is computed for each beat as the product of stroke volume and heart rate. The result is called 'model cardiac output' in the remainder of the paper.

Model total systemic peripheral resistance is obtained as follows. For the first simulated beat, an initial value for peripheral resistance is assumed and mean arterial pressure and cardiac output are computed with this first value in place. The ratio of pressure to cardiac output for this first beat defines a new resistance value, which is used in the model for the next beat, and so forth. Within five beats from the start, the model resistance usually stabilizes to the systemic peripheral resistance value. This self-adaptation scheme remains permanently active so that changes in systemic peripheral resistance that occur are followed by the model. This is possible because systemic peripheral resistance changes slowly, with a time constant which is typically approximately 10 s.

Pressure transducers were clamped to the operating table to keep their correct hydrostatic height with respect to heart level. When height changes occurred they were noted but level correction was not attempted. Continuous flush devices prevented clotting at the catheter tips. The resonant frequency of the system in use at each location was measured in the laboratory and ranged between 15 and 25 Hz. Before each comparison with thermodilution the arterial waveform quality was visually inspected and the catheter was flushed if slow rising upstrokes took more than 100 ms to reach a maximum. The close observation of pressure pulsation quality was facilitated by a static on-screen display similar to the one shown in Figure 1. Damping of the waveform was continuously monitored by software and an alerting message was displayed whenever risetime increased beyond 150 ms. Occasionally, however, a slow rising waveform had physiological causes and led to a false alarm.

Thermodilution method

Thermodilution cardiac output measurements were performed with system controlled by a personal computer, and included an iced injectate container (CO-SET, Baxter-Edwards, Irvine, CA, USA), a proprietary, motor driven injectate syringe, a thermodilution Swan-Ganz catheter (Baxter), and a COM-2 cardiac output computer (Baxter). The start of the ventilatory cycle was read from the ventilator output or, if unavailable, detected from the capnogram waveform. At precisely timed, variable delays from the start of the ventilatory cycle injections of 10 ml of iced glucose solution 5% were triggered automatically. Delays were spread equally over the ventilatory cycle,[21 22] each 25% of the cycle for a series of four injections (Maastricht), each 33% for a series of three injections (San Diego and Leuven). The three or four cardiac output determinations were averaged to obtain one single value for average cardiac output in that period. For this technique to work optimally, the haemodynamic state and respiratory rate must be stable during the series.[21]

Data acquisition

The software we used is an online real-time version of the BEATFAST offline program, called MODELFLO.EXE (TNO, Academic Medical Centre, Amsterdam, The Netherlands) dated May 1997. It automates all actions and records all haemodynamic data relevant to the study. As cardiac output in a patient can be quite variable, it is important to acquire the data from each method simultaneously. Computer storage of the sampled arterial pressure waveform and beat-to-beat derived haemodynamic data for each comparison started one full respiratory cycle before a thermodilution injection, continued for as many respiratory cycles until at least 18 s had passed, and stopped after one additional respiratory cycle. This resulted in an average recording time of 30 s for each single thermodilution measurement. The digital output of the COM-2 device was also stored, including values for cardiac output, blood temperature, injectate temperature, computation constant, and warning and error codes. This procedure was repeated for the remaining injections in a series with a period of five ventilatory cycles allowed between any two measurements. A series of three or four measurements thus took between 150 and 210 s. Although the MODELFLO monitor ran continuously, waveform samples were recorded only during thermodilution series.

Data analysis

To compare model and thermodilution cardiac output, model cardiac output was first averaged over the beats recorded during an injection. Then the three or four model and thermodilution values per series were each averaged to obtain one single data pair (CO_{mf}, CO_{td}) for further analysis. Both values estimate the average cardiac output during a series.

The same set of comparison data pairs was analysed twice.

1. In a first analysis, model cardiac output (CO_{mf}) was used as is with the model based on the patient's gender, age, height, and weight. This is called uncalibrated.
2. In a second analysis model, cardiac output ($CO_{\kappa 1}$) was made equal to thermodilution cardiac output in the first series after induction, through multiplication by a patient individual calibration factor, $\kappa_1 = CO_{td1}/CO_{mf1}$. This reduces the uncertainty in the patient's aortic diameter, because of the high standard deviation of the age and gender based population average. As the first data pair in each patient, would, therefore, be defined to have zero difference it was excluded from further analysis.

With the second method, we mainly investigated the ability of the model to track changes in cardiac output.

A trend score was computed for each patient and also for the group of patients. The trend score is derived from the changes in consecutive cardiac output values. If both methods simultaneously indicate a positive trend, the changes compare positively and a positive score is counted. If both show a negative trend, they again compare positively. When the changes in cardiac output are in opposite directions they compare negatively and a negative score is counted (see Fig. 6 for examples). Ideally, only positive scores are present. Separate scores were made for all consecutive changes regardless of size, and also for changes where consecutive thermodilution cardiac output values differed by at least 0.5 litre min^{-1}, which is considered clinically relevant.

A trend analysis was performed to spot any systematic trends in cardiac output and in the difference between the methods.[24] This was done by plotting the mean of the model and thermodilution cardiac outputs and their difference averaged over the group and for each half hour of the operation. The calibration pair for each patient was not included.

Haemodynamic stability was verified by analysis of mean arterial pressure and heart rate during a thermodilution series. Stability was considered absent if mean arterial pressure and heart rate averaged per injection period deviated more than 5% from their series average.[22] Severe, persistent arrhythmias during thermodilution measurement was also considered to be absence of stability. If stability was not present, the series was excluded from further analysis. Periods with balloon pump counterpulsation had to be discarded as the model method did not properly recognize the heart beats.

The range ratio of haemodynamic values during an operation was computed as the ratio of the largest to the smallest value that was measured in a patient. Thus, if a lowest mean arterial pressure of 60 and a highest of 120 mm Hg were measured the range ratio was 120/60=2. For two-pressure ranges one 30–90 mm Hg (difference=60, ratio=3) and another 80–140 mm Hg (difference=60, ratio 1.75), the first is more important than the second, because of the non-linear properties of the aorta. The ratio was computed for cardiac output, heart rate, mean arterial pressure, and total peripheral resistance as it has been suggested that these parameters may affect the accuracy of methods such as the model method.

Statistical analysis

We gathered data in three clinical centres in three countries with slightly different anaesthetic regimen, in female and male patients, with changing patient condition during the operation. We studied how these factors might affect cardiac output comparison by testing correlations and differences between cardiac output methods. We used the statistical package BMDP version 7, program 1V and 5V (BMDP, Los Angeles, CA, USA). If either variable is not significantly dependent on centre or patient gender, the data can be pooled to get more reliable statistics.

Computation of limits of agreement was the principal method of analysis with differences in data pairs plotted against their average.[23] The agreement between model and thermodilution cardiac output is computed as the bias (mean), with limits of agreement computed as bias ±2 SD[23] when differences followed normal distributions. Normality was tested with the Kolmogorov–Smirnov one-sample test. The coefficient of variation was computed as CV=(SD/mean)×100%. Data averages are given as mean (SD). Statistical significance was considered present when $P<0.05$.

Results

In 18 female and 36 male patients a total of 566 thermodilution series were obtained during a median operation time of 4 h 30 min. Inadequate haemodynamic stability caused rejection of 59 thermodilution series. Insufficient pressure signal quality caused rejection of 14 series. Thermodilution problems caused rejection of three series. Thus, 490 series of acceptable quality remained. In

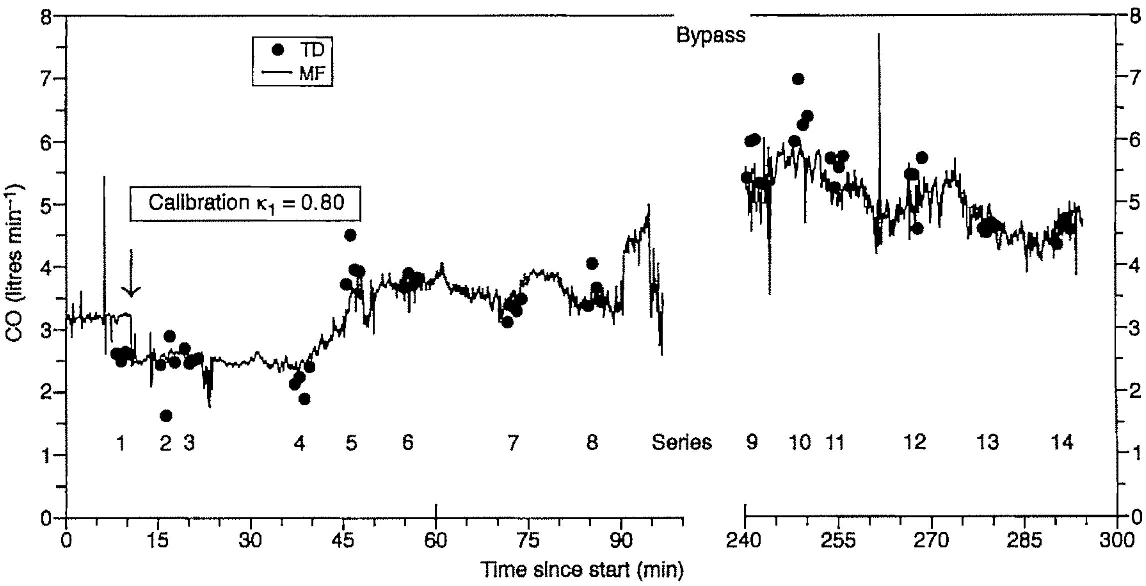


Fig 2 Trend plot in patient 54. This patient was selected because she had a large ratio between highest and lowest cardiac output. The individual thermodilution measurements, not yet averaged over each series of four, are shown as solid dots. Series are numbered from 1 to 14. Continuous model cardiac output is shown as an eight-beat average, which is uncalibrated until the first thermodilution series is completed, at the arrow.

Table 1 Summary of patient details and haemodynamic data. In the columns unit: the unit used to express the numerical values; mean, average values obtained as indicated; SD, standard deviation; range, minimum left and maximum value. Parameters: κ_1, model calibration factor based on first determinations; MAP, mean arterial pressure; HR, hear rate; TPR, total peripheral resistance from MAP/CO_{td}; CO_{td}, thermodilution cardiac output; CO_{mf}–CO_{td}, difference between uncalibrated model and thermodilution cardiac output; $CO_{\kappa 1}$–CO_{td}, difference between calibrated model and thermodilution cardiac output. Above the line the data first averaged per patient and then pooled for the group, below the line all the measurements pooled

Variable	Units	Mean	SD	Range
Patient characteristics, *n*=54				
Age	yr	62	9	43–78
Height	cm	169	8	153–188
Weight	kg	74	8	55–92
κ_1		0.95	0.18	0.62–1.45
Patient means				
MAP	mm Hg	79	7	65–98
HR	min^{-1}	73	11	50–107
TPR	dyn s cm^{-5}	1350	300	817–2534
CO_{td}	litre min^{-1}	4.9	0.9	3.0–7.7
CO_{mf}–CO_{td}	litre min^{-1}	10.3	0.9	–1.5–2.4
$CO_{\kappa 1}$–CO_{td}	litre min^{-1}	–0.1	0.2	–0.7–0.3
Pooled data				
MAP	mm Hg	78	12	39–114
HR	min^{-1}	73	19	39–147
TPR	dyn s cm^{-5}	1332	415	531–2978
CO_{td}	litre min^{-1}	5.0	1.3	2.0–9.3
$CO_{\kappa 1}$–CO_{td}	litre min^{-1}	–0.1	0.5	–2.1–1.6

each patient data from before and after bypass were available.

Figure 2 shows an example of a trend graph of model and thermodilution cardiac output of each injection in patient 54. Although substantial changes in cardiac output occurred between the 14 series, the tracking of thermodilution by model cardiac output was close. Individual thermodilution measurements show scatter within some series of four measurements, but no measurement was rejected.

Table 1 summarizes patient data and selected haemodynamic variables. These include thermodilution cardiac output and the differences between model and thermodilution cardiac output before and after model calibration. Taking averages for each patient and then pooling the 54 patient results, or pooling all 490 series resulted in only marginal differences for the mean values. Standard deviations and ranges were less if patient averages were taken first. Thus, pooling all series, the greatest range ratios for mean arterial pressure, heart rate, thermodilution cardiac output, and systemic peripheral resistance were 3, 4, 5, and 6:1, respectively. Within patients, mean arterial pressure ranged over 2:1 or greater ratios in four of the 54 patients, heart rate in 13, thermodilution in 12, and total peripheral resistance in 20 of the 54 patients. Thus, the haemodynamic state was far from constant within and between patients and peripheral resistance was the least stable.

The mean calibration factor κ_1 was 0.95, which was significantly different from 1.00. The calibration factor was not related to any patient or haemodynamic variable recorded. The cardiac output bias of +0.32 litre min^{-1} before calibration decreased to –0.13 litre min^{-1} and became non-significant. The standard deviation of the differences of 1.0 litre min^{-1} is halved after calibration to 0.47 litre min^{-1}. The differences were not associated with any of the other haemodynamic variables, including systemic peripheral resistance.

The Kolmogorov–Smirnov test for the difference between model and thermodilution cardiac output did not indicate a significant deviation from a normal distribution. No significant differences between clinical centre and between gender were found either before or after once calibrating the model. The data from both patient sexes and from the three clinical centres, could therefore, be pooled. Both methods, however, indicated a highly significant increase in cardiac output towards the end of surgery. This is shown as half hour averages pooled for the group in Figure 3. The difference between the methods is similarly plotted in the bottom trace but shows no significant trend away from zero. Of 436 trends in cardiac output, 354 (81%) were scored in the same direction by both methods. Of 204 trends in thermodilution cardiac output greater than 0.5 litre min^{-1}, 199 (97%) were indicated correctly in direction by model cardiac output.

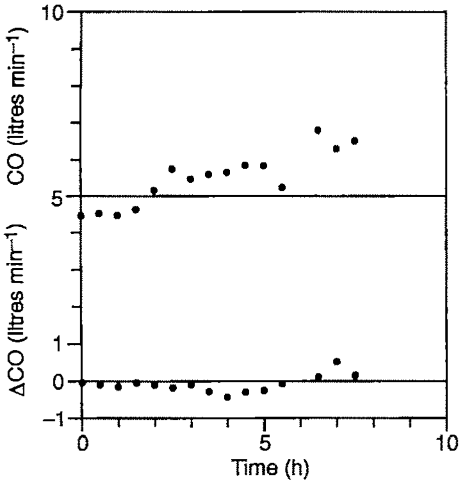


Fig 3 Trend plots of cardiac output and cardiac output difference *vs* time from induction of anaesthesia. Cardiac output is the mean of model and thermodilution values. The data of all patients are pooled per half hour and plotted at the start of each half hour. Data points are plotted only when at least three values were available for that half hour. Cardiac output increases significantly with time and post bypass. Cardiac output difference showed no significant trend.

Figure 4 shows uncalibrated model *vs* thermodilution cardiac output for the calibrating cardiac output pair of each patient. Clear differences in the absolute level of cardiac output were present up to +2 and −1.5 litre min^{-1}. In the scattergram four patients are marked with a '×' symbol. They had the greatest cardiac output and systemic peripheral resistance range ratio, and smallest and largest cardiac output and are shown individually in Figure 5, demonstrating the marked variability of cardiac output between and within patients. In Figure 5, the line through the origin and the calibrating point is also shown for the two patients with the highest range ratios. Clearly, individual estimates are closer to this line than to the line of identity, which shows that differences from thermodilution are largely systematic. They can thus be corrected by a calibration factor that alters the slope of the line towards unity.

The cardiac output of patient 31 is plotted as a trend chart in Figure 6a, with mean arterial pressure, heart rate, and total peripheral resistance included. Again, the model method bias appears insensitive to changes in these variables even though the systemic peripheral resistance range ratio is 3.4:1. This patient also has one of the lowest calibration factors, κ_1=0.66, yet tracking was not affected. The duration of the operation on patient 45 in Figure 6b is unusually long. The calibration factor, κ_1=0.97, but the plot is of values before calibration. After bypass, the cardiac output increases are associated with infusions of 450 ml of autologous whole blood and 250 ml of packed cells nitroglycerine and dopamine

Figure 7 summarizes in four panels the pooled results before and after calibration of the model. The two left hand panels show scatter plots of the 490 (top panels) and 436 series (bottom panels). The points lie closer to the line of identity after calibration. The right hand panels show Bland–Altman plots. The 15 largest negative differences, those below the −2 sd line in the bottom right diagram, were obtained in eight patients and were all recorded immediately after bypass. They do not depend on the value of cardiac output.

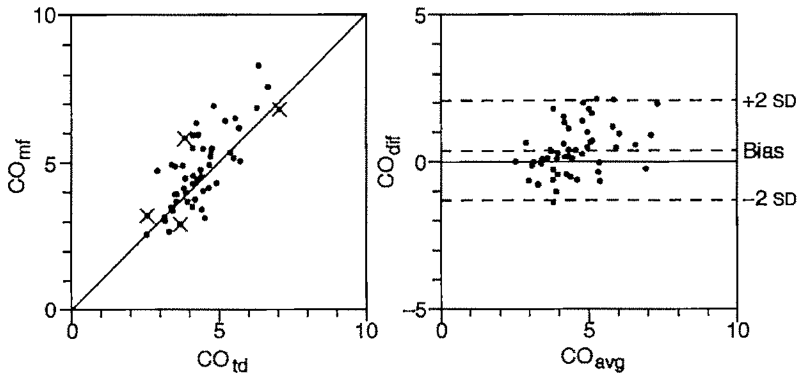
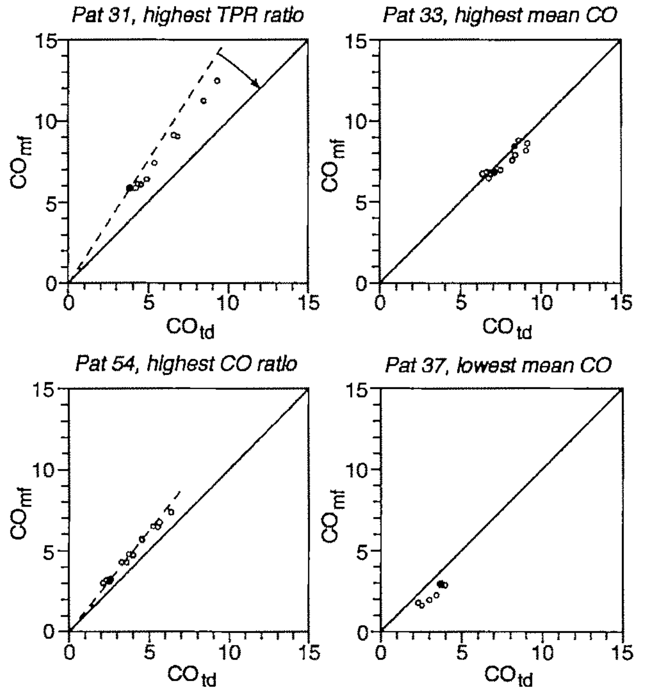


Fig 4 The model *vs* thermodilution cardiac output pairs for the calibration (the first) series in the 54 patients. In the Bland–Altman plot CO_{dif} is CO_{mf}–CO_{td}, CO_{avg} is their mean. The crosses indicate four patients shown in full in Fig. 5.



Pat 31, highest TPR ratio

Pat 33, highest mean CO

Pat 54, highest CO ratio

Pat 37, lowest mean CO

Fig 5 Scattergram of uncalibrated model and thermodilution cardiac output in four patients selected for lowest (3.2) and highest (7.6 litre min^{-1}) mean cardiac output and greatest cardiac output (3.0:1) and systemic peripheral resistance (3.4:1) range ratio. Calibration turns the dashed line for patient 31 in the direction of the arrow onto the line of identity. In this patient the other points move below the line of identity which will result in a negative bias after calibration. The solid dot (●) indicates the calibration pair.

Discussion

We found that the Modelflow method can reliably track directional changes in thermodilution cardiac output in cardiac surgery patients. Cardiac output can be monitored quantitatively and continuously with little error *only* after an initial calibration of the model to an individual patient. Acquiring such relatively precise data required several precautions.

A precise thermodilution method

An important factor in this research was a good reference for comparison. Individual thermodilution cardiac output estimates show substantial scatter in their values even under stable haemodynamic and ventilatory conditions.[25] Four quickly repeated thermodilution estimates of cardiac output may differ more than 1 litre min^{-1}. In such circumstances, an average of a number of random injections does not allow a true mean cardiac output estimate. When injections are synchronized with ventilation, however, not by a fixed or a random but by a systematically varied phase equally spread over the ventilatory cycle, much closer estimates of true mean cardiac output can be obtained[21] by eliminating ventiliation effects. Precise timing of the injections requires a trigger synchronized with ventilation, and computer control. Precisely measured injections over a repeatably short time period requires a motor driven syringe.[26] We used a system for thermodilution cardiac output that is simple but not generally available.

Quality control of arterial pressure measurement

A second important factor was adequate control of the quality of measurement of intra-arterial pressure. All pressure transducers were calibrated against the same standard. Zeroing was done semi-automatically and occasionally checked, although never adjusted during a surgery. The pressure pulsation risetime was constantly monitored with a simple computer algorithm. Visual inspection before each thermodilution series was also the rule. Changes in the hydrostatic level of the pressure transducer with respect to the heart affect model cardiac output. Theoretically, when arterial pressure is artificially high because of a low position of the transducer, model cardiac output is slightly but measurably reduced, and vice versa. Tilting of the operating table caused height changes up to ±15 cm, or approximately 10 mm Hg, and which we did not correct. As height changes were in both directions, and as the errors introduced are small, they have little effect on overall statistics in view of the other sources of error.[14]

Patient selection

A third important factor was patient selection. All patients probably had patent aortic valves and no aortic aneurysms. An aneurysm affects a patient's aortic compliance. A patent aortic valve is required for proper model cardiac output computation as the model computes forward flow into the aorta and in regurgitation ignores backward flow. Thus, model cardiac output will be systematically larger than thermodilution which estimates the net flow as forward minus backward flow. We cannot exclude the possibility that some patients had a small undetected valve leakage, or that such leakage occurred at some times during surgery. If so, this will increase the inaccuracy of the comparison.

Haemodynamic stability

Suspension of major surgery during a series was been a fourth important factor. Haemodynamic stability, however, is not a prerequisite for a correct model cardiac output. Changes in cardiac output are as reliably estimated by the model during arrhythmias and various cardiovascular manoeuvres as when heart rate and rhythm and circulatory volume distribution were stable (J.J. van Lieshout, personal communication).

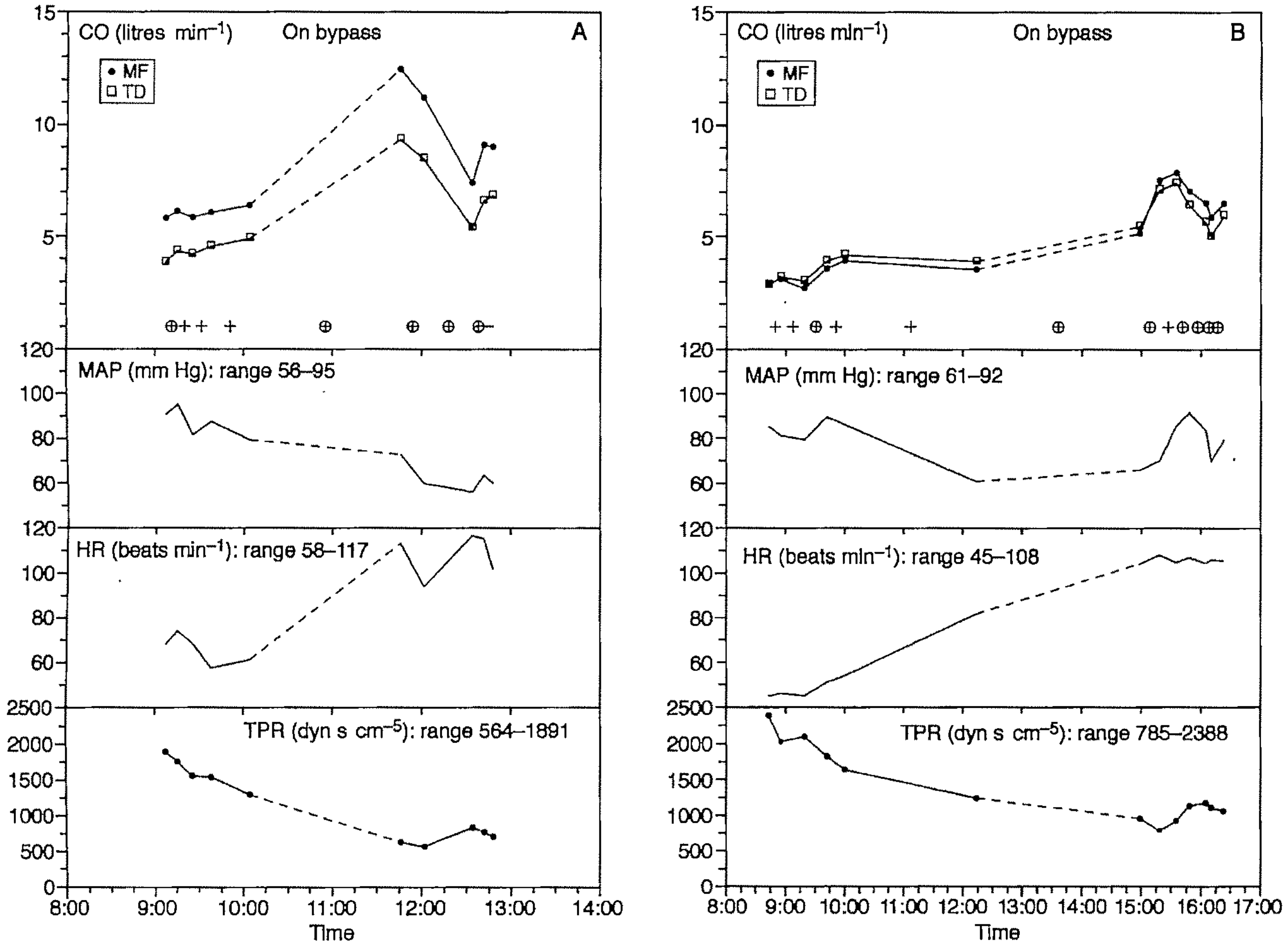


Fig 6 (A) Trendplot of patient 31 with the highest systemic vascular resistance range ratio, and (B) trend plot of patient 45 with a long operation. MF, uncalibrated model cardiac output; TD, thermodilution cardiac output; MAP, mean arterial pressure; HR, heart rate; TPR, total systemic vascular resistance computed as MAP/TD. The + signify correct, the – incorrect indication of thermodilution trend by the model method. The ⊕ signify correct and ⊖ incorrect, trends for thermodilution trends greater than 0.5 litre min^{-1} between consecutive determinations. (A) The trendscore is 9 trends of which 8 are indicated correctly (9/8), 5 trends greater than 0.5 litre min^{-1} which are all correct (5/5). (B) These scores are (12/12) and (7/7).

Model calibration

Differences between uncalibrated model and thermodilution cardiac output in individual patients are small in most but substantial and unreliable in some. The standard deviation of the difference, 19%, is similar to that of a single thermodilution estimate,[22] to that of bioimpedance,[13] or ultrasound Doppler flow velocity in the aorta,[1–6] or continuous thermodilution,[10 11] but the differences are largely systematic, as this study shows (Figs 5 and 6). Thus, averaging a number of measurements tends not to improve the precision of model cardiac output much. When interest is in monitoring percentage changes in cardiac output from a control level, calibration is not needed and the fact that model errors are principally systematic is an advantage.[16] In other circumstances calibration is necessary. As the trend plot of differences between the methods (Fig. 3) does not show a trend away from zero a single calibration per operation seems adequate. The calibration does not change on the second day of monitoring compared with from the first.[17]

Pharmacological agents

The administration of fluids, vasoactive drugs, and cardiac stimulants was not changed from normal routine for this study. These will change arterial pressure, heart rate, ejection time, contractility, cardiac output, and peripheral resistance. As a consequence, the variations in heart rate, cardiac output, and peripheral resistance were substantial (Table 1), yet tracking precision of model cardiac output appeared unaffected. Nitroglycerine or sodium nitroprusside were administered principally after sternotomy and after cardiopulmonary bypass. Thus, if these agents affected model error, it should be evident in these parts of the operation. No important trend in the differences away from zero is seen in Figure 3, and is confirmed by the absence of significance in the differences analyses (see Statistics methods).

In another study[3] changes in total peripheral resistance were suggested to reduce the tracking ability of a commercial device. The close tracking of our model method during

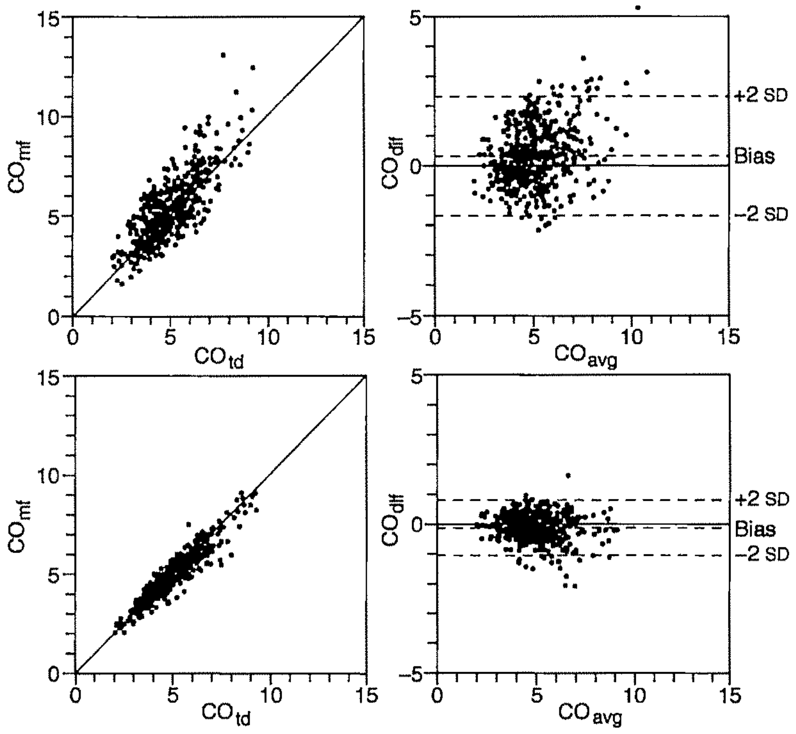


Fig 7 Diagrams showing the data pairs in all 54 patients before (top, n=490) and after (bottom, n=490–54=436) calibration on the first series after induction of anesthesia. In the Bland–Altmanplot CO_{dif} either CO_{mf}–CO_{td} before, or CO_{KI}–CO_{td} after calibration; CO_{avg} is their mean. The dashed lines indicate the bias and limits of agreement between methods.

changes in peripheral resistance might have been facilitated by the self-adapting model peripheral resistance, as explained under Methods.

Exclusion of data

We performed 566 series of thermodilution estimates and rejected 76, based on pre-set criteria. This study was set up to investigate bias and precision of the model method. To achieve this goal the precision of the comparisons should not be impaired by a poor reference value or by inadequate arterial pressure recordings.

Single thermodilution estimates are inaccurate as they are strongly affected by baseline temperature changes and the waxing and waning of right heart cardiac output with ventilation.[27] Thus, averaging of several random estimates is needed to obtain reasonable accuracy. Our goal for the cardiac output reference was to achieve near 5% precision. Given the precision of single estimates of 17%[22 25 28 31] we would have to average some nine estimates as inaccuracy decreases in proportion to the square root of the number. However, using the ventilatory phase-spreading technique, inaccuracy reduces in proportion to the number of estimates and three estimates would improve precision from 17 to 6%.[21 22] For the averaging technique to work, the haemodynamic, conditions should be stable during the series. To judge stability we could have used model cardiac output but this method was under test. We, therefore, used mean arterial pressure and heart rate as easily obtainable measures. Between the thermodilution estimates in a series, we allowed each parameter to deviate maximally 5% from the series average. Inspection of the rejected series suggest that the 5% criteria might have been too strict, as we rejected some apparently adequate series in terms of cardiac output comparison. In another study, under different circumstances, the limit was relaxed to 10% deviation, and acceptable results were still obtained.[16]

The arterial pressure waveform used as input for the haemodynamic model should ideally have been aortic pressure. This waveform differs from radial artery pressure in shape. As radial artery pressure is what is used clinically the model had to accept this. As shown in another study[14] the use of radial artery pressure modifies the model flow waveform but by integrating the flow over systole, to obtain stroke volume, waveform purity becomes less relevant. Radial artery pressures in some patients, however, may deteriorate in mean level and pulse amplitude for a period after bypass in comparison to aortic pressures.[29] The pressure difference between aorta and radial artery is usually almost negligible at 0–2 mm Hg. After bypass it can become as great as 10 mm Hg for mean and more than twice that for systolic pressures in six of 38 patients,[29] caused by an increase in pressure gradient in the proximal arteries of uncertain cause. With 15 outliers in eight patients all recorded immediately after bypass, this emphasizes importance of a reliable arterial pressure as input for the model method. Due to warming of the patient post bypass, with substantial changes in thermal baseline, thermodilution may also be unreliable in this critical period.

Discussion of errors

In an editorial Gardner[30] proposed that objective criteria be established for judging the precision of cardiac output measurement methods. Critchley and Critchley,[31] in trying to establish such objective criteria state that: if a 'new' method is to replace an older, established method, the new method should itself have errors not greater than the older method.

Thermodilution is the reference cardiac output method in almost all studies, as in the present one. A single thermodilution estimate of cardiac output has a probable percentage error standard deviation or coefficient of variation, further called 'error', of 15–20%.[22,25,28,31] A triplicate, randomly injected thermodilution has an error of 10% as the result of averaging.[31] When the new method's error, n, is acceptable if it is the same as that of the method to be replaced, r, the error of the comparison, c, can be computed with Pythagoras' law as $c^2=n^2+r^2$ or $c=\sqrt{n^2+r^2}$.[31] This computation requires the errors to be statistically independent of each other. Usually, however, we have the error of the comparison and an estimate of the error of the reference method. The error of the new method is then computed as $n=\sqrt{c^2-r^2}$.

Approximately, the error we found between the uncalibrated model and thermodilution cardiac output is 19% (Table 1). Our reference cardiac output used the phase-spreading injection technique, which has only 17/3~6% error. The conclusion is that uncalibrated model cardiac output has an error of $\sqrt{19^2-6^2}=18\%$. If a triplicate random thermodilution is to be replaced by another technique, uncalibrated model cardiac output is not the method of choice as it is not sufficiently precise (18 *vs* 10% required) as a standalone method.

After model calibration, the error of subsequent comparisons decreases to 9% (Table 1). With 6% error of the thermodilution reference, the calibrated model cardiac output has a probable error of $\sqrt{9^2-6^2}=7\%$. This is almost as good as a triplicate phase-spreading thermodilution (7 *vs* 6%) and could thus almost replace it.[31] It is definitely better than a triplicate random thermodilution (7 *vs* 10%).

Positioning of the model method

Response time is a variable to be specified for a continuous cardiac output method.[30] For the model method it is the duration of one beat, and even after eight-beat averaging, response time is measured in seconds, not minutes.[9]

Invasiveness is another aspect to be considered.[27] Clearly, the model method as studied here, requires an invasive signal: radial artery pressure. Thus, although as a method it is not more invasive, it is not non-invasive. In a remarkable study, however, Hirschl and colleagues[15] used non-invasive finger arterial pressure as input to the same model as used in the present study in critically ill patients in an emergency department. They also used the phase-spreading thermodilution technique as a precise reference although no mention is made of rejection of data if haemodynamic conditions were unstable. No mention is made of the possibility of calibration on the first series. Expressed as cardiac index, their results are quite similar to ours before calibration, including a similar bias and a small number of outliers beyond the limits of agreement.

The present study adds to Hirschl and co-workers' results the use in cardiac surgery patients; emphasizes the tracking ability of the model method after calibration; indicates the insensitivity of the model method to changes in mean arterial pressure, heart rate, and systemic peripheral resistance as caused by vasoactive agents, cardiac stimulants or improved heart function after surgery; and confirms that differences between model and thermodilution cardiac output before calibration are not related to age, gender, underlying diagnosis, or body mass index. Differences are because of uncertainty about the diameter of the individual patient's aorta, not apparently related to any obvious patient characteristic.[20] By using invasive arterial pressure in the present study we avoided uncertainty about non-invasively obtained arterial pressure pulsations. Even though mean arterial pressure was measured well, non-invasively, in a similar setting in similar patients,[32] this does not automatic guarantee that non-invasive pressure pulsations as input to the model are also correct. In view of the similarity in results between the present and Hirschl and colleagues' study, however, we support their comment that differences between model and thermodilution cardiac output *before calibration* (our emphasis) are substantially caused by the uncertainty in the model calibration for each patient.

In a non-invasive study in young adult healthy volunteers who underwent a laboratory tilt table procedure, model stroke volume with non-invasive finger arterial pressure as input tracked changes in thermodilution to within 10% error during head-up tilt. Head-up tilt and standing induce blood volume shifts in the body with 50 and 30% reductions in stroke volume on average.[16] Although not obtained in critically ill patients we interpret these results as confirmation that non-invasive tracking of changes in cardiac output may be valuable in the future.

The model simulation method could be tested for cardiac output tracking in other categories of patients, including children for which little information is yet available, and more extensively than is already done,[15,16] with non-invasive finger pressure as input.

Conclusions

In patients without aortic abnormalities, undergoing coronary artery bypass surgery, the continuous monitoring of *changes* in cardiac output by simulation of a non-linear, self-adapting model of arterial input impedance is reliable and response to changes in cardiac output is almost immediate. After an initial thermodilution calibration for each individual patient, it has near zero bias and, a 7% error, and a precision sufficient to replace subsequent conventional triplicate thermodilution. Close control of the quality of peripheral artery pressure measurement is necessary. In our automated set-up this is facilitated by computer detection of damped waveforms. Vasoactive drugs and cardiac stimulants in the usual doses do not appear to affect the ability to track the changes in cardiac output thus induced.

Acknowledgement

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References

1 Warner HR, Swan HJC, Connolly DC, Tompkins RG, Wood EH. Quantitation of beat-to-beat changes in stroke volume from the aortic pulse contour in man. *J Appl Physiol* 1953; **5**: 495–507

2 Wesseling KH, De Wit B, Weber JAP, Smith NT. A simple device for the continuous measurement of cardiac output. *Adv Cardiovasc Phys* 1983; **5**: 16–52

3 Rödig G, Prasser C, Keyl C, Liebold A, Hobbhahn J. Continuous cardiac output measurement: pulse contour analysis *vs* thermodilution technique in cardiac surgical patients. *Br J Anaesth* 1999; **82**: 525–30

4 Shimaoto H, Kito H, Kawazoe K, Fujita T, Shimamoto Y. Transoesophageal Doppler echocardiographic measurement of cardiac output by mitral annulus method. *Br Heart J* 1992; **68**: 510–5

5 Siegel LC, Pearl RG. Noninvasive cardiac output measurement: troubled technologies and troubled studies. *Anesth Analg* 1992; **74**: 790–2

6 Segal J, Gaudiani V, Nishimura T. Continuous determination of cardiac output using a flow directed Doppler pulmonary artery catheter. *J Cardiothorac Vasc Anesth* 1992; **5**: 309–15

7 Doi M, Morita K, Ikeda K. Frequently repeated Fick cardiac output measurements during anesthesia. *J Clin Monit* 1990; **6**: 107–12

8 Yelderman ML, Ramsey MA, Quinn MD, Paulsen AW, McKown RC, Gillman PH. Continuous thermodilution cardiac output measurement in intensive care unit patients. *J Cardiothorac Vasc Anesth* 1992; **6**: 270–4

9 Aranda M, Mihm FG, Garrett S, Mihm MN, Pearl RG. Continuous cardiac output catheters. Delay in *in vitro* response time after controlled flow changes. *Anesthesiology* 1998; **89**: 1592–5

10 Mihm FG, Gettinger A, Hanson III CW, *et al.* A multicenter evaluation of a new continuous cardiac output pulmonary artery catheter system. *Crit Care Med* 1998; **26**: 1346–50

11 Zöllner C, Polasek J, Kilger E, *et al.* Evaluation of a new continuous thermodilution cardiac output monitor in cardiac surgical patients: a prospective criterion standard study. *Crit Care Med* 1999; **27**: 293–8

12 Shoemaker WC, Wo CCJ, Bishop MH, *et al.* Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. *Crit Care Med* 1994; **22**: 1907–12

13 Haryadi DG, Westenskow DR, Critchley LAH, *et al.* Evaluation of a new advanced thoracic bioimpedance device for estimation of cardiac output. *J Clin Monit* 1999; **15**: 131–8

14 Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *Appl Physiol* 1993; **74**: 2566–73

15 Hirschl MM, Binder M, Gwechenberger M, *et al.* Noninvasive assessment of cardiac output in critically ill patients by analysis of the finger blood pressure waveform. *Crit Care Med* 1997; **25**: 1909–14

16 Harms MPM, Wesseling KH, Pott F, *et al.* Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin Sci* 1999; **97**: 291–301

17 Jellema WT, Wesseling KH, Groeneveld ABJ, Stoutenbeek CP, Thijs LG, van Lieshout JJ. Continuous cardiac output in septic shock by simulating a model of aortic input impedance. *Anesthesiology* 1999; **90**: 1316–28

18 Westerhof N, Elzinga G, Sipkema P. An artificial arterial system for pumping hearts. *J Appl Physiol* 1971; **31**: 776–81

19 Toorop GP, Westerhof N, Elzinga G. Beat-to-beat estimation of peripheral resistance and arterial compliance during pressure transients. *Am J Physiol* 1987; **21**: H1275–83

20 Langewouters GJ, Wesseling KH, Goedhard WJA. The static elastic properties of 45 human thoracic and 20 abdominal aortas *in vitro* and the parameters of a new model. *J Biomech* 1984; **17**: 425–35

21 Jansen JRC, Versprille A. Improvement of cardiac output estimation by the thermodilution method during mechanical ventilation. *Intensive Care Med* 1986; **12**: 71–9

22 Jansen JRC, Schreuder JJ, Settels JJ, Kloek JJ, Versprille A. An adequate strategy for the thermodilution technique in patients during mechanical ventilation. *Intensive Care Med* 1990; **16**: 422–5

23 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–10

24 Altman DG, Royston JP. The hidden effect of time. *Stat Med* 1988; **7**: 629–37

25 Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW. Thermodilution cardiac output measurement. Effect of the respiratory cycle on its reproducibility. *JAMA* 1985; **253**: 2240–2

26 Nelson LD, Houtchens BA. Automatic vs manual injections for thermodilution cardiac output determinations. *Crit Care Med* 1982; **10**: 190–2

27 Popovitch MJ, Hoffman WD. Noninvasive cardiac output monitoring. *Crit Care Med* 1997; **25**: 1783–4

28 Stetz CW, Miller RG, Kelly GE. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Resp Dis* 1982; **125**: 1001–4

29 Pauca AL, Hudspeth AS, Wallenhaupt SL, *et al.* Radial artery to aorta pressure difference after cardiopulmonary bypass. *Anesthesiology* 1989; **70**; 935–41

30 Gardner RM. Continuous cardiac output: how accurate and how timely? *Crit Care Med* 1998; **26**: 1302–3

31 Critchley LAH, Critchley JAJH. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit* 1999; **15**: 85–91

32 Hirschl MM, Binder M, Herkner H, *et al.* Accuracy and reliability of noninvasive continuous finger blood pressure measurement in critically ill patients. *Crit Care Med* 1996; **24**: 1684–8

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Continuous intra-jugular venous blood-gas monitoring with the Paratrend 7 during hypothermic cardiopulmonary bypass[†]

H. Endoh[1]*, T. Honda[1], S. Oohashi[1], Y. Nagata[2], C. Shibue[2] and K. Shimoji[2]

[1]Department of Emergency and Critical Care Medicine and [2]Department of Anesthesiology, Niigata University Faculty of Medicine, 1-757 Asahimachi, Niigata 951-8150, Japan

**Corresponding author*

We measured the accuracy of the continuous intra-vascular blood-gas monitoring system (Paratrend 7, PT7) placed in the jugular venous bulb in 18 adult patients having cardiac or aortic surgery with hypothermic cardiopulmonary bypass (CPB). After induction of anaesthesia, a PT7 sensor was inserted through a 20-gauge venous catheter into the right jugular venous bulb. Blood samples were drawn from the venous catheter and measured with a blood gas analyser (BGA). Five to eight paired measurements using the PT7 and blood samples were made per patient, and bias and precision were calculated for each patient using the Bland-Altman method. The ranges for the blood sample measurements were: pH 7.12 to 7.59, $P\text{CO}_2$ 3.7 to 9.6 kPa, $P\text{O}_2$ 3.5 to 16.0 kPa, oxygen saturation 40 to 99%, bicarbonate 18.6 to 34.4 mmol l^{-1}, and base excess –7.8 to 12.5 mmol l^{-1}. Bias and precision values were 0.014/0.071 for pH, 0/0.90 kPa for $P\text{CO}_2$, and –0.16/1.18 kPa for $P\text{O}_2$. These values were comparable with those previously made on arterial blood. However, precision for oxygen saturation in each patient varied 2.3 to 23.6% (95% CI: 6.3 to 12.9%), which was unsatisfactory for clinical measurements. Deep hypothermia (~19.6°C) and marked haemodilution (~13.5%) during CPB did not influence the reliability of the PT7 sensor. Thus, we concluded that continuous intra-jugular venous blood-gas monitoring is clinically feasible using the PT7 and may provide valuable information during CPB.

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Brain injury is a serious adverse complication following cardiac surgery with cardiopulmonary bypass (CPB). Several aetiologies have been proposed; an imbalance between cerebral oxygen supply and demand during CPB may contribute to brain injury. Continuous measurement of jugular venous oxygen saturation using a fibreoptic oximetric catheter has been used during or after CPB to assess cerebral oxygen balance.[1–3]

When increased oxygen extraction by the brain can no longer completely compensate for decreased oxygen supply, cerebral oxygen consumption will decrease and anaerobic metabolism with lactate production will result.[4] These features may not be detected adequately by measuring changes in oxygen saturation or oxygen tension ($P\text{O}_2$); measurements of pH and carbon dioxide tension ($P\text{CO}_2$) in the jugular venous blood may more completely indicate changes in brain oxygenation.

The Paratrend 7 system (PT7) (Biomedical Sensors, High Wycombe, UK) incorporates four different sensors: $P\text{O}_2$ is measured with a miniaturized Clark-type electrode, $P\text{CO}_2$ and pH are measured with two optical fibres, and blood temperature is determined by a thermocouple. In addition, oxygen saturation, bicarbonate, and base excess are automatically computed from these variables. The four sensor elements are housed in a heparin-coated microporous polyethylene tubing approximately 0.5 mm in diameter, which can be passed through a 20-gauge catheter.

Acceptable accuracy and good clinical performance of the PT7 sensors in arterial blood have been demonstrated during surgery[5–10] and in the intensive care unit.[11–15] We know of only one anecdotal report that describes the use of the PT7 in the jugular bulb of a patient with subarachnoid haemorrhage.[16] We evaluated the accuracy and clinical feasibility of continuous intra-jugular blood-gas monitoring

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with the PT7 in adult patients undergoing cardiac or aortic surgery with hypothermic CPB.

Methods

After institutional approval, patients undergoing coronary artery bypass graft (CABG) surgery (n=12) or aortic surgery (n=8) under hypothermic CPB were enrolled. Written informed consent was obtained directly from 19 patients, and a close relative gave assent for one patient because the patient was intubated and sedated. Patients with cerebrovascular disease, uncontrolled hypertension (systolic pressure >150 mm Hg and/or diastolic pressure >95 mm Hg), or diabetes mellitus were excluded from the study. Premedication consisted of intramuscular atropine 0.5 mg and morphine 0.1 mg kg^{-1} for elective cases or intramuscular atropine 0.5 mg for emergency cases, given 45–60 min before transfer to the operating room. Anaesthesia was induced with midazolam 0.1–0.2 mg kg^{-1} i.v., fentanyl 30 μg kg^{-1}, and pancuronium bromide 0.15 mg kg^{-1} and maintained with a continuous infusion of fentanyl (10 μg kg^{-1} h^{-1}), supplemented with sevoflurane (0.5–1.0 MAC). Muscular relaxation was maintained with intermittent doses of 4 mg pancuronium bromide i.v. The trachea was intubated, and the lungs were mechanically ventilated to maintain normocapnia with a mixture of oxygen and air ($F\text{I}_{\text{O}_2}$ 0.5–0.85). At the beginning of CPB, midazolam 0.2 mg kg^{-1} and pancuronium bromide 4 mg were administered. During CPB, no anaesthetics were given. A radial artery catheter was inserted to measure arterial pressure and sample arterial blood. Electrocardiogram, pulmonary artery pressure, oesophageal and bladder temperature, pulse oximeter saturation, and end-tidal CO_2 and sevoflurane concentration (Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland) were measured.

After induction of anaesthesia, a 8.0Fr introducer sheath (Arrow International, Inc., Reading, PA, USA) for a 7.5Fr pulmonary artery catheter (Arrow International, Inc.) and a 7Fr triple lumen catheter (Arrow International, Inc.) were inserted through the right internal jugular vein. In addition, a 5.1 cm long, 20-gauge venous catheter (Insyte, Becton Dickinson Inc., Franklin Lakes, NJ, USA) was inserted cephalad more than 2 cm apart from the insertion sites of the above two catheters. For continuous monitoring of jugular venous blood, the PT7 sensor was advanced more than 15 cm through the catheter into the jugular bulb, and adjusted to lie in the jugular bulb using fluoroscopy. *In vitro* calibration was performed before the insertion. After stabilization of the sensor in the jugular bulb, *in vivo* calibration between the sensor and the blood gas analyser (BGA) was carried out, and no further calibrations were done. Blood samples (0.5 ml) were drawn via a Y-connection attached to the venous catheter at a rate of 1 ml min^{-1} regardless of body temperature or the status of CPB and measured with a blood gas analyser (Corning 280 with Corning 2500 co-oximetry, Bayer Medical Ltd, Tokyo, Japan) within 2 min. According to the manufacturer, when used with the usual calibration frequencies (one-point calibrations every 30 min and two-point calibrations every 2 h) the precision expected is 0.002 pH units, 0.25 kPa, 0.17 kPa, and 0.58% for pH, $P\text{CO}_2$, $P\text{O}_2$, and oxygen saturation, respectively, over the following range of measurements: pH 7.0–7.6 pH units, $P\text{CO}_2$ 2.7–13.2 kPa, and $P\text{O}_2$ 2.7–20.0 kPa.

All data are presented at 37°C without temperature correction, and the PT7 data were stored in a personal computer (Macintosh PowerBook 5300cs, Apple Computer, Tokyo, Japan) via a RS-232C port every 1 min for subsequent analysis.

Cardiopulmonary bypass

A non-pulsatile pump flow rate of 2.2–2.6 litres min^{-1} m^{-2} was maintained using a membrane oxygenator and a 40-μm arterial filter. Perfusion pressure was maintained at 50–90 mm Hg using either chlorpromazine 0.3–1.0 mg kg^{-1} i.v. or phenylephrine 0.1–0.5 mg i.v. Oesophageal temperature during aortic cross-clamp was maintained in the range of 25 to 30°C for CABG surgery or 15 to 20°C for aortic surgery. Pa_{CO_2} was adjusted to 4.5–5.3 kPa without temperature correction. Selective cerebral perfusion was maintained at a flow rate of 5–10 ml kg^{-1} min^{-1} for all patients who underwent aortic surgery.

Statistical analysis

We used a statistical package (SPSS 9.0 for Windows, Base and Advanced models; SPSS Inc., Chicago, IL, USA). All data are presented as mean and SD. Hydrogen ion concentration ([H^+] nmol $litre^{-1}$) was calculated from the value of pH. Bias (mean of the differences of the values measured by the PT7 minus the blood sample values) and precision values (1.96 SD of the differences) for each variable were calculated for each patient by the Bland-Altman method.[17] Simple linear regression analysis of each variable was made by the least-squares method. The paired data were then divided into three subgroups according to the value of bladder temperature or haematocrit. Bias and precision for each variable were also calculated in each of the three subgroups, and the bias values were compared using one-way analysis of variance. When significance was found, Fisher's protected least significant difference test was used as a *post hoc* comparison procedure. P values <0.05 were considered significant.

Results

Data from two patients who underwent aortic surgery were excluded because of sensor malfunction, and results from 18 patients are reported (mean age 66 yr (range 44–79); female/male ratio 5:13). One patient who underwent aortic replacement remained comatose and died on the second postoperative day. There were no complications related to

Table 1 Bias and precision values for each variable in each patient and overall bias, precision, and regression values

Patient number	Samples	pH (pH units)	[H$^+$] (nmol litre^{-1})	PCO$_2$ (kPa)	PO$_2$ (kPa)	Saturation (%)	Bicarbonate (mmol litre^{-1})	Base excess (mmol litre^{-1})
1	7	–0.016/0.082	–1.8/8.0	0.39/0.89	–0.67/0.08	–2.9/7.4	6.52/6.79	5.13/6.05
2	5	0.025/0.024	2.2/2.2	0.26/0.61	0.18/0.77	–1.2/3.7	0.02/1.86	–0.34/1.27
3	5	0.026/0.065	2.1/5.4	0.13/0.65	0.02/1.68	–2.5/7.0	1.28/5.80	–0.02/4.63
4	8	0.026/0.104	3.6/13.7	–0.06/0.53	–0.24/1.26	0/2.3	0.31/4.19	–0.46/3.99
5	7	0.025/0.122	3.7/18.3	–0.10/1.11	–0.35/1.99	–3.6/14.6	2.13/5.13	0.30/3.62
6	5	0.017/0.049	1.8/4.8	–0.11/1.27	–0.54/1.09	–6.9/2.4	0/2.55	–0.40/3.40
7	5	–0.020/0.096	–1.4/7.0	–0.05/0.91	0.53/1.27	1.3/12.7	–0.42/3.22	0.06/2.79
8	5	–0.010/0.057	–0.9/4.6	–0.21/0.83	–0.48/1.64	–1.7/6.6	1.38/3.91	0.65/3.35
9	6	0.008/0.073	1.0/6.9	0.03/0.74	–0.21/1.51	–1.2/3.4	2.60/5.01	2.03/4.38
10	5	0.011/0.067	1.4/6.7	–0.17/0.88	–0.22/0.88	–3.7/7.0	–2.24/4.41	–1.88/5.12
11	5	0.038/0.047	4.9/6.6	0.19/0.82	–0.20/0.74	–4.9/9.0	–1.48/5.62	–0.60/2.55
12	5	–0.003/0.069	–0.3/7.2	–0.30/0.50	0.32/1.99	4.1/23.6	–1.46/6.74	–1.76/3.57
13	5	0.028/0.071	2.5/6.6	–0.66/0.56	–0.18/1.86	0.1/4.2	0.50/4.99	–1.00/2.37
14	6	–0.002/0.104	–0.2/9.4	–0.36/1.28	–0.38/0.74	–3.6/6.4	–0.10/7.07	0.32/6.66
15	5	0.022/0.102	2.3/9.9	0.21/1.88	–0.36/0.22	–3.7/15.3	–1.26/6.00	–2.54/5.71
16	5	0.033/0.029	3.5/3.6	0.07/0.83	–0.38/0.43	–4.1/4.2	–0.28/2.48	–0.85/2.38
17	6	0.023/0.045	4.3/5.3	0.41/0.81	0.33/0.65	3.3/6.4	3.12/6.12	3.36/6.59
18	6	0.025/0.078	2.6/7.9	0.36/1.05	–0.12/1.65	–1.5/15.6	1.80/8.41	1.50/3.31
Overall bias/precision		0.014/0.071	1.7/7.5	0/0.90	–0.16/1.18	–1.8/9.6	0.69/5.02	0.19/3.99
Regression (R^2)		0.82	0.79	0.81	0.89	0.87	0.56	0.74

Table 2 Bias and precision values for each variable in the three different subgroups based on bladder temperature (A) or haematocrit (B) (n=101). All values are expressed as bias/precision (1.96SD)

A	Bladder temperature (°C)			P value for bias
	≥35	<35 to ≥30	<30	
Samples (n=101)	39	30	32	
Temperature (°C)	0.4/1.4	0.3/3.1	0.8/7.1	0.61
pH (pH units)	0.023/0.076	–0.004/0.082	0.014/0.084	0.18
PCO$_2$ (kPa)	0.02/0.96	–0.02/0.80	–0.12/1.22	0.15
PO$_2$ (kPa)	–0.12/1.17	–0.16/1.43	–0.42/1.36	0.15

B	Haematocrit (%)			P value for bias
	≥25	>25 to ≥20	<20	
Samples (n=101)	38	32	31	
Temperature (°C)	0.4/2.0	0.8/6.1	0.4/4.6	0.77
pH (pH units)	0.012/0.076	0.024/0.088	0.008/0.078	0.29
PCO$_2$ (kPa)	0.03/0.96	–0.15/0.93	0.006/1.14	0.32
PO$_2$ (kPa)	–0.19/1.44	–0.12/1.32	–0.40/1.10	0.24

insertion of the sensor. All other patients survived and were discharged without clinically obvious brain injury. The mean durations of CPB, surgery, and anaesthesia were181 min (range 109–353), 353 min (range 247–545), and 464 min (range 315–690), respectively.

Five to eight paired measurements with the PT7 and blood samples were made on each patient, with a total of 101 paired measurements. The ranges of each variable measured from the blood sample were: pH 7.12 to 7.59, PCO$_2$ 3.7 to 9.6 kPa, PO$_2$ 3.5 to 16.0 kPa, oxygen saturation 40–99%, bicarbonate 18.6 to 34.4 mmol litre^{-1}, and base excess –7.8 to 12.5 mmol litre^{-1}. Bias and precision values for each variable in each patient and overall bias, precision, and regression values are given in Table 1.

During this study, bladder temperature and haematocrit varied between 19.6 and 37.4°C, and between 13.5 and 41.1%, respectively. Bias and precision values for each variable in the three subgroups are given in Table 2. Bias values were not significantly different, and precision values were comparable in all three subgroups (Table 2).

A trace of the jugular venous measurements by the PT7 in a 65-year-old, female patient (patient 4 in Table 1) who underwent CABG surgery is given in Fig. 1.

Discussion

This study found good accuracy of the PT7 in the jugular venous bulb during hypothermic CPB; overall bias and

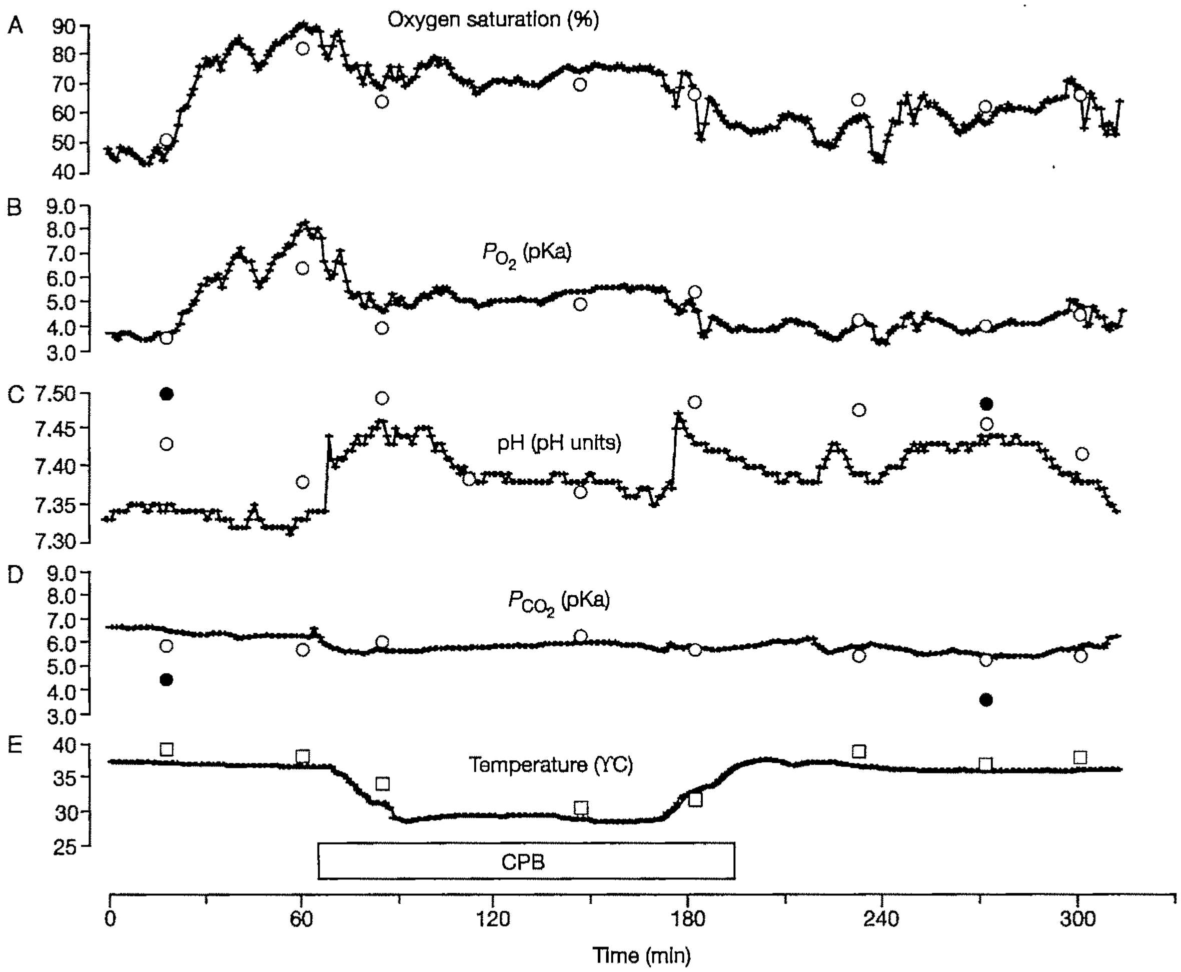

Fig 1 A tracing of the jugular venous oxygen saturation (A), P_{O_2} (B), pH (C), P_{CO_2} (D), and temperature (E) measured by the Paratrend 7 in a 65-yr-old, female patient who underwent coronary artery bypass grafting surgery with an uneventful clinical course. Open circles represent the corresponding values of jugular venous blood measured by a blood gas analyser, closed circles represent the values of arterial blood measured by a blood gas analyser, and open squares represent values of bladder temperature. CPB=cardiopulmonary bypass.

Table 3 Comparison of bias and precision values between the Paratrend 7 and blood gas analyser with other published data. CPB=cardiopulmonary bypass

Author	Monitoring site	Samples	Clinical setting	pH (pH units)	P_{CO_2} (kPa)	P_{O_2} (kPa)
Venkatesh and colleagues[5]	Artery	157	Cardiac surgery with CPB	0.01/0.06	0.53/0.35	0.5/6.0
Zollinger and colleagues[6]	Artery	138	Differential lung ventilation	–0.017/0.065	0.31/0.76	0.38/9.52
Ishikawa and colleagues[7]	Artery	84	Differential lung ventilation	0.00/0.02	0.12/0.41	–0.13/5.33
Myles and colleagues[10]	Artery	55	Lung transplantation	0.006/0.10	–0.21/1.57	–2.93/14.4
Venkatesh and colleagues[11]	Artery	158	Intensive care unit	0.01/0.06	0.2 /1.4	0.4 /6.8
Nunomiya and colleagues[12]	Artery	62	Intensive care unit	0.002/0.018	0.07 /0.27	–0.21/2.67
Weiss and colleagues[13]	Artery	150	Pediatric intensive care unit	0.006/0.024	–0.10/0.62	0.25/2.28
Hatherill and colleagues[14]	Artery	100	Pediatric intensive care unit	0.02/0.06	–0.44/0.74	0.04/0.87
Present study	Jugular vein	101	Cardiac surgery with CPB	0.014/0.071	0/0.90	–0.16 /1.18

precision values for pH, P_{CO_2}, and P_{O_2} were comparable with previous studies made on arterial blood (Table 3).[5–14] In addition, a better bias or precision value for P_{O_2} was observed in this study, which may be attributable to a narrow range of jugular venous P_{O_2}. Indeed, several studies have demonstrated a high accuracy of the P_{O_2} sensor when it is placed in a radial artery with a range of P_{O_2} less than 20 kPa.[7 11 12] Furthermore, the 95% confidence intervals (CI) for bias and precision for each variable were 0.006 to 0.022 and 0.058 to 0.084 pH units for pH, –0.14 to 0.14 and 0.73 to 1.06 kPa for P_{CO_2}, and –0.32 to 0 and 0.90 to 1.45 kPa for P_{O_2}, respectively; these values were satisfactory for clinical measurements. However, overall bias and precision values for oxygen saturation were –1.8/9.6%, and the precision for each patient varied from 2.3 to 23.6% (95% CI: 6.3 to 12.9%), which is not clinically acceptable. Similarly, Hatherill and colleagues[14] reported poor precision for oxygen saturation (9.5%) despite the smallest bias and precision for Po_2 in children with cyanotic heart disease. The PT7 does not measure oxygen saturation directly, but calculates it from $P\text{o}_2$, resulting in the significant discrepancy of precision between $P\text{o}_2$ and oxygen saturation.

During this study, bladder temperature and haematocrit varied from 19.6°C to 37.3°C and from 13.5 to 41.1%, respectively. However, these large changes in temperature or haematocrit did not influence the reliability of the intra-jugular pH, $P\text{o}_2$, or $P\text{co}_2$ sensor (Table 2). These findings support those of Venkatesh and colleagues,[5] who showed that the PT7 in a radial artery functioned well during CPB; unfortunately, ranges of temperature and haematocrit during CPB were not shown in their study.

The threshold value for the jugular venous $P\text{o}_2$ has not yet been determined. In volunteers breathing 100% nitrogen, slowing of EEG was observed when the jugular venous $P\text{o}_2$ decreased to 2.5 kPa.[18] Taking the difference between normal jugular venous $P\text{o}_2$ (4.7–6.2 kPa) and the critical level described above ($\geqslant$2.2 kPa), the bias, precision, and 95% CI for Po_2 presented in this study are acceptable for clinical decision making. Similarly, there are no available human data describing critical values for jugular venous pH and $P\text{co}_2$. However, in several human studies when the PT7 was inserted into brain tissue[19 20] or in cerebrospinal fluid,[21] trends showed a concomitant increase in $P\text{co}_2$ and decrease in pH, along with a decrease in $P\text{o}_2$ during sustained brain ischemia[19 20] or after brain death.[21] Continuous measurement of jugular venous pH and $P\text{co}_2$ together with $P\text{o}_2$ using the PT7 may give more information on the balance between brain oxygen supply and demand than the currently used fibreoptic oximetric catheter.

Sensor malfunction occurred in two of eight patients who underwent aortic surgery with selective cerebral perfusion, but not in 12 patients who underwent CABG surgery. Postoperative fluoroscopy showed kinking of the sensors, which had not been seen preoperatively. All malfunctions occurred before the start of selective cerebral perfusion, and perfusion itself did not contribute to malfunctions. However, the patient's head was moved for surgical positioning, presumably resulting in deflection of the sensors.

In conclusion, we describe good accuracy of the pH, $P\text{o}_2$, and $P\text{co}_2$ sensors of the PT7 in the jugular venous bulb, comparable to previous findings with arterial blood. Mild to deep hypothermia and marked haemodilution during CPB did not affect the reliability of the sensors. There were no complications attributable to the insertion of the sensor. Thus, continuous jugular venous blood-gas monitoring is clinically feasible using the PT7 and may provide valuable information during hypothermic CPB. However, large studies would be needed to demonstrate clinical improvement.

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References

1 Croughwell ND, Newman MF, Blumenthal JA, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58**: 1702–8

2 Nakajima T, Kuro M, Hayashi Y, Kitaguchi K, Uchida O, Takaki O. Clinical evaluation of cerebral oxygen balance during cardiopulmonary bypass: on-line continuous monitoring of jugular venous oxyhemoglobin saturation. *Anesth Analg* 1992; **74**: 630–5

3 Souter MJ, Andrews PJ, Alston RP. Jugular venous desaturation following cardiac surgery. *Br J Anaesth* 1998; **81**: 239–41

4 Schell RM, Cole DM. Cerebral monitoring: Jugular venous oximetry. *Anesth Analg* 2000; **90**: 559–66

5 Venkatesh B, Clutton-Brock TH, Hendry SP. Evaluation of the Paratrend 7 intravascular blood gas monitor during cardiac surgery: comparison with the C4000 in-line blood gas monitor during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1995; **9**: 412–9

6 Zollinger A, Spahn DR, Singer T, *et al.* Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery. *Br J Anaesth* 1997; **79**: 47–52

7 Ishikawa S, Makita K, Nakazawa K, Amaha K. Continuous intra-arterial blood gas monitoring during oesophagectomy. *Can J Anaesth* 1998; **45**: 273–6

8 Palmer TE, Cumpston PH, Foster WJ, Jones RD. Continuous intra-vascular blood gas analysis during aortic aneurysm repair: the Paratrend 7. *Anaesth Intensive Care* 1995; **23**: 200–2

9 Myles PS, Story DA, Higgs MA, Buckland MR. Continuous measurement of arterial and end-tidal carbon dioxide during cardiac surgery: $P_{a\text{-ET}}$ CO_2 gradient. *Anaesth Intensive Care* 1997; **25**: 459–63

10 Myles PS, Buckland MR, Weeks AM, Bujor M, Moloney J. Continuous arterial blood gas monitoring during bilateral sequential lung transplantation. *J Cardiothorac Vasc Anesth* 1999; **13**: 253–7

11 Venkatesh B, Clutton Brock TH, Hendry SP. A multiparameter sensor for continuous intra-arterial blood gas monitoring: a prospective evaluation. *Crit Care Med* 1994; **22**: 588–94

12 Nunomiya S, Tsujimoto T, Tanno M, Matsuyama N, Ohtake K, Kubota T. Clinical evaluation of a new continuous intra-arterial blood gas monitoring system in the intensive care setting. *J Anesth* 1996; **10**: 163–9

13 Weiss I K, Fink S, Edmunds S, Harrison R, Donnelly K. Continuous arterial gas monitoring: initial experience with the Paratrend 7 in children. *Intensive Care Med* 1996; **22**: 1414–7

14 Hatherill M, Tibby SM, Durward A, Rajah V, Murdoch IA. Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease. *Br J Anaesth* 1997; **79**: 665–7

15 Tobias JD, Connors D, Strauser L, Johnson T. Continuous pH and Pco_2 monitoring during respiratory failure in children with the Paratrend 7 inserted into the peripheral venous system. *J Pediatr* 2000; **136**: 623–7

16 Menzel M, Soukup J, Rieger A, Roth S, Radke J, Burkert W. Continuous measurement of jugular venous blood gas. A case of subarachnoid bleeding. *Anaesthetist* 1997; **46**: 329–34

17 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–10

18 Meyer JS, Gotoh F, Ebihara S, Tomita M. Effects of anoxia on cerebral metabolism and electrolytes in man. *Neurology* 1965; **15**: 892–901

19 Hoffman WE, Charbel FT, Edelman G, Hannigan K, Ausman JI. Brain tissue oxygen pressure, carbon dioxide pressure and pH during ischemia. *Neurol Res* 1996; **18**: 54–6

20 Hoffman WE, Charbel FT, Munoz L, Ausman JI. Comparison of brain tissue metabolic changes during ischemia at 35° and 18°C. *Surg Neurol* 1998; **49**: 85–9

21 Venkatesh B, Boots R, Tomlinson F, Jones RDM. The continuous measurement of cerebrospinal fluid gas tensions in critically ill neurosurgical patients: a prospective observational study. *Intensive Care Med* 1999; **25**: 599–605

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Cerebral hypoperfusion in immediate postoperative period following coronary artery bypass grafting, heart valve, and abdominal aortic surgery

S. M. Millar[1], R. P. Alston[2 3] *, P. J. D. Andrews[2 4] and M. J. Souter[5]

[1]Department of Anaesthesia, The Alfred Hospital, Prahran Melbourne, Victoria, Australia. [2]Anaesthesia, Critical Care and Pain Medicine Section, Department of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh, UK. [3]Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK. [4]Department of Anaesthesia, Western General Hospital, Edinburgh, UK. [5]Department of Neuroanaesthesia, Southern General Hospital, Glasgow, UK

**Corresponding author*

Perioperative levels of jugular bulb oxyhaemoglobin saturation (Sj_{O_2}) and lactate concentration (Lj), and postoperative duration of Sj_{O_2}<50% were compared between patients undergoing coronary artery bypass grafting (CABG) (*n*=86), heart valve (*n*=14) and abdominal aortic (*n*=16) surgery. Radial artery and jugular bulb blood samples were aspirated after induction of anaesthesia, during re-warming on cardiopulmonary bypass (CPB) (36°C), on arrival in the intensive care unit (ICU) and, subsequently, at 1, 2 and 6 h after ICU admission. Most patients having heart surgery were hypocapnic at 36°C on CPB. Following CABG and heart valve surgery, many patients were hypocapnic whereas after abdominal aortic surgery, most were hypercapnic. During CPB and postoperatively, Sj_{O_2} and Lj were significantly correlated to Pa_{CO_2} and the arterial concentration of lactate (La) respectively ($P<0.05$). After correction for arterial carbon dioxide tension (Pa_{CO_2}) and La, there were no significant changes in Sj_{O_2} or Lj on CPB. Postoperatively, having corrected for Pa_{CO_2}, there were significant effects on Sj_{O_2} over all groups as a result of time from surgery ($P<0.001$) and its interaction with operation type ($P<0.001$). Following correction for La, there were no postoperative effects on Lj. No significant differences ($P=0.2$) in duration of Sj_{O_2}<50% existed between patients undergoing CABG (1054 (82) min), abdominal aortic (893 (113) min) and heart valve (1073 (91) min) surgery. The lack of significant reciprocal effects on Lj combined with the frequency of hypocapnia and strong influence of Pa_{CO_2}on Sj_{O_2}, suggest that Sj_{O_2}<50% during CPB and after cardiac surgery represents hypoperfusion as a consequence of hypocapnia rather than cerebral ischaemia.

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Despite much research, a common mechanism of injury for the brain damage that is associated with coronary artery bypass grafting (CABG) surgery has yet to be determined.[1] This failure may in part be because of the focus of research on cardiopulmonary bypass (CPB) as the epoch when damage occurs. We have found, using fibreoptic measurements of jugular bulb oxyhaemoglobin saturation (Sj_{O_2}), that many patients appear to experience episodes, often multiple and sometimes prolonged, of cerebral hypoperfusion (Sj_{O_2}<50%) in the early postoperative period following CABG surgery.[2] Although cerebral hypoperfusion has been reported intraoperatively,[3–5] we have found the average duration of postoperative Sj_{O_2}<50% to be in excess of six times longer.[2] Therefore, if some brain damage results from occurrences during CPB,[3] then the far more prolonged postoperative cerebral hypoperfusion may consequently cause more damage. However, it is not known whether postoperative cerebral hypoperfusion is a phenomenon that only follows cardiac surgery as if so, this would be a strong indication that it causes cerebral damage.

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In other recent work,[6] we have found levels of the arteriovenous difference in lactate concentration (AVDL) during the re-warming phase of CPB that, in patients who have suffered head injuries, would equate with profound cerebral ischaemia or infarction.[7 8] In addition, we have found evidence of cerebral hypoperfusion using a combination estimate, the lactate-oxygen index (LOI).[4 6 9] The cerebral arteriovenous difference in oxygen content (AVDO$_2$), AVDL and LOI are related to factors that influence cerebral blood flow and oxygen delivery including arterial carbon dioxide tension (Pa_{CO_2}), concentration of arterial lactate, arterial oxyhaemoglobin saturation (Sa_{O_2}), mean arterial pressure (MAP) and arterial haemoglobin concentration (Hba).[9–12] Postoperative cerebral hypoperfusion may be caused by deranged levels of these variables. However, determination of AVDO$_2$ and LOI are error prone.[13] Moreover, AVDL, AVDO$_2$ and LOI are both mathematically coupled to, and not statistically independent from, factors that may influence them including Hba, Sa_{O_2} and the concentration of arterial lactate.[13–15] By contrast to these derived measures, Sj_{O_2} and concentrations of jugular bulb lactate (Lj) are robust and statically independent estimates of the adequacy of cerebral perfusion.[13]

Consequently, the primary aim of this study was to establish whether postoperative cerebral hypoperfusion, as estimated by levels of Sj_{O_2}, Lj and duration of $Sj_{O_2}<50\%$, is subsequent only to cardiac surgery by comparing patients undergoing CABG, heart valve, and abdominal aortic surgery. The secondary aim was to investigate the effects of the concentration of arterial lactate, Pa_{CO_2}, MAP, Hba, and Sa_{O_2} upon Sj_{O_2} and Lj.

Methods

The Local Ethics Committee approved the study. Patients were excluded if they had a history of previous cerebrovascular accident, transient ischaemic attack or diabetes mellitus.

Anaesthesia and postoperative management

For all groups, the anaesthetic techniques were according to individual consultant practice. Approximately 1 h before surgery, all patients were premedicated with temazepam 20–40 mg or lorazepam 1–2 mg p.o. either alone or in combination with morphine 10–15 mg with or without atropine 0.3–0.6 mg i.m. Anaesthesia was induced with thiopental 1–3 mg kg^{-1}, etomidate 0.1–0.2 mg kg^{-1} or propofol 1–2 mg kg^{-1} in addition to fentanyl 4–10 μg kg^{-1} or remifentanil 1–2 μg kg^{-1} i.v. Neuromuscular blockade was obtained with pancuronium 0.1 mg kg^{-1} or rocuronium 0.9 mg kg^{-1}. Anaesthesia was maintained with 1–2% isoflurane, propofol target controlled infusion (TCI) 2–3 μg ml^{-1} and remifentanil 0.02–0.1 μg kg^{-1} min^{-1}, or morphine 0.25 mg kg^{-1} h^{-1} and midazolam 0.04 mg kg^{-1} h^{-1} i.v.

In patients undergoing abdominal aortic surgery, a low thoracic epidural catheter was placed. Epidural 0.125% bupivacaine with either fentanyl 2 μg ml^{-1} or ketamine 166 μg ml^{-1} was administered during and after surgery. Anaesthesia was induced with propofol 1–2 mg kg^{-1} and neuromuscular blockade was obtained with atracurium 0.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with either 0.5–2% isoflurane or propofol TCI 2–3 μg ml^{-1} along with nitrous oxide and oxygen.

Following surgery, patients having cardiac surgery were transferred to the intensive care unit (ICU) where mechanical ventilation was weaned and the trachea extubated according to a previously described protocol.[2 9] Tracheal extubation in those patients having abdominal aortic surgery was undertaken before transfer to a general surgical high dependency unit (HDU).

Cardiopulmonary bypass

Cardiopulmonary bypass was used for all patients undergoing CABG or heart valve surgery. The CPB circuit and its management have been described in detail.[6 9 16] In particular, the circuit was primed with 2 litres of lactated Ringer's solution and 50 mmol sodium bicarbonate was used. Thermal management on CPB was according to surgical practice: the lowest nasopharyngeal temperature ranged from 28.7 to 35.2°C in the patients having heart valve surgery and from 27.1 to 36.5°C in patients undergoing CABG surgery. As was our practice when the study was undertaken, re-warming was carried out with the heat exchanger set at no more than 10°C above the patient's nasopharyngeal temperature, and not above 42°C.

Fibreoptic Sj_{O_2} and haemodynamics

All patients had radial artery cannulation and central venous line placement for pressure monitoring. A Baxter Edslab 4F (Baxter Healthcare Corporation, Edwards Critical-Care Division, Irvine, CA, USA) double lumen oximetric catheter was placed preferentially into the right internal jugular bulb using a previously described technique.[2] The position of the catheter tip in the jugular bulb was confirmed on a plain lateral neck x-ray carried out after surgery. The first co-oximeter measurement was used to calibrate the fibreoptic catheter *in vivo* according to the manufacturer's instructions. Following surgery, calibration was repeated using the first post-operative blood sample result. If the continuous Sj_{O_2} reading differed by more than 5% from the co-oximeter reading, or if there was a change in haemoglobin concentration of greater than 1.8 g dl^{-1}, the catheter was re-calibrated.

Fibreoptic Sj_{O_2} measurements were recorded every minute from the start of surgery until its completion. Postoperative recording was continued for 18 h after arrival in the ICU for the cardiac surgery patients or from arrival in the recovery area for the abdominal aortic surgery patients.

Data were logged on computer and then converted to a format compatible with the Edinburgh Data Browser (Medical Research Council Head Injuries Clinical Research Initiative, Western General Hospital, Edinburgh, UK). A Kolormon 7250 Monitoring System (Kontron Instruments Ltd., Watford, Herts, UK) was used in the CABG and heart valve surgery patients, both intra- and postoperatively. In patients undergoing abdominal aortic surgery, the Critical Care Explorer (Baxter Healthcare Ltd, Wallingford Road, Compton, Newbury, Berkshire, UK) was used to measure Sj_{O_2} throughout but other haemodynamic parameters were monitored using the Component Monitoring System (Hewlett Packard Ltd, Uxbridge, Middlesex, UK) intraoperatively and the Cardiocap2 (Datex Ohmeda Ltd, Hatfield, Herts, UK) postoperatively. Cerebral hypoperfusion was defined, using methodology developed for assessment of neurological outcome in patients with head injuries, as a $Sj_{O_2}<50\%$ for at least 5 min.[17]

Blood samples

Blood samples were aspirated into heparinized syringes from the radial artery and jugular bulb following induction of general anaesthesia; during re-warming on CPB when nasopharyngeal temperature reached 36°C (CABG and heart valve surgery groups only); on arrival in ICU or recovery area; and, subsequently, at one, two and six hours. Sampling times were based upon a preliminary ranging study that identified the time points as having the highest frequency of $Sj_{O_2}<50\%$ in the first 18 h after CABG surgery.[9] Each blood sample was measured in the same three analyzers: (i) bench oximeter (IL 482 CO-oximeter, Instrumentation Laboratory, Lexington, MA, USA) which measured the concentration and saturation of oxyhaemoglobin; (ii) blood gas analyzer (ABL 4, Radiometer Ltd, Copenhagen, Denmark) which measured the partial pressure of oxygen and carbon dioxide, and (iii) lactate analyser (YSI 2300 Stat G/L, YSI Inc., Yellow Springs, OH, USA) which measured the lactate concentration.

Sample size

Calculation of sample size was based upon a mean duration of $Sj_{O_2}<50\%$ to be 14% of the total monitored time in the postoperative period following CABG surgery.[2] It was assumed that postoperative $Sj_{O_2}<50\%$ does not occur following major abdominal vascular surgery but a 1% duration was used to give a margin for error. Assuming a one sided percentage point of the normal distribution and f=3/4, 46 patients in the abdominal aortic surgery group and 92 in the CABG group would give an 80% power of detecting a significant difference with alpha set at 0.05 in the duration of $Sj_{O_2}<50\%$.

Statistical analysis

Statistical analysis was performed using SPSS 6.1 (SPSS Inc., Chicago, IL, USA) running on a Macintosh G3 personal computer with OS 8.6. Non-normally distributed data (duration) were transformed using the natural logarithm. A probability of 0.05 was used as the level of significance in all analysis.

As we have previously described, method comparison analysis was used to compare bench and fibreoptic measurements of Sj_{O_2}.[16] Duration of $Sj_{O_2}<50\%$ was analysed using general factorial analysis of variance with the operation grouping entered as a factor on three levels.[15] As there were between group differences in age and timing of tracheal extubation, these variances were controlled by entering them as covariates. To examine the influence of the duration of CPB, this was also entered into the model with the abdominal aortic surgery group entered as zero.

Repeated measures multivariate analysis of variance (MANOVA) was used to analyse the discrete measurements of Sj_{O_2} and Lj and these were entered as within-subject variables.[15] Operation grouping was entered as a factor and, to examine their influence on $Sj_{O_2}$and Lj, Pa_{CO_2}, MAP, Sa_{O_2} and Hba were entered as varying covariates. To control for any differences between the groups, age and duration of CPB were entered as constant covariates. Using a full factorial model, a sequential approach was taken to decomposing the sum of squares. First, this adjusts covariates for all factors and interactions and then each factor is adjusted for all covariates, factors and preceding interactions. Post-hoc analysis was performed using paired and unpaired Student's t-test as appropriate.

Results

From February 1997 to January 1998, 116 patients, including those from two preliminary reports,[9 16] gave written informed consent and of these, six failed to enter the study because of re-scheduling of surgery. Less than the planned population were recruited because of technical difficulties adapting the data logging system and lower than expected throughput of patients undergoing vascular surgery. Eight patients were excluded. Causes for exclusion were co-oximeter failure; inability to aspirate jugular line intraoperatively; postoperative cardiovascular instability precluding blood sampling and, inability to aspirate from or premature removal of the arterial line postoperatively. Patients undergoing abdominal aortic surgery tended to be older and tracheal extubation occurred earlier than in the other two groups (Table 1). One patient had a cerebrovascular accident and two died from cardiac failure in the CABG surgery group.

Method comparison analysis

Whilst the limits of agreements between bench and fibreoptic measurements of Sj_{O_2} were reasonable following surgery, agreements were wide during CPB. For this reason, fibreoptic oximetry measurements were excluded from the analysis of Sj_{O_2} during CPB (Table 2).

Discrete variables

Discrete variables are summarized in Table 3. Throughout the study, patients in all surgical groups experienced a wide range of Pa_{CO_2}. During the re-warming phase of CPB, the majority of patients undergoing CABG and heart valve surgery were hypocapnic. On arrival on the ICU, and at 1 h postoperatively, many patients having CABG and heart valve surgery were also hypocapnic whereas the majority of patients having abdominal aortic surgery were hypercapnic.

Repeated measures MANOVA revealed that, both during CPB and in the postoperative period, there were significant positive correlations between Sj_{O_2} and $PaCO_2$ and Lj and the arterial concentration of lactate (Table 4). Examination of the regression coefficients revealed that for a 1 kPa decrease in Pa_{CO_2} the average decrement in Sj_{O_2} was 4% during CPB and 9% following surgery. For an increase in the arterial concentration of lactate of 1 mmol, Lj increased by an average of 0.9 mmol during CPB and postoperatively. None of the other covariates correlated significantly with Sj_{O_2} or Lj.

Table 1 Physical characteristics of patients and operative details. CABG= coronary artery bypass grafting surgery; Aortic=abdominal aortic surgery; Valve=heart valve surgery; Excluded=patients excluded; Number of CABGs=number of coronary artery bypass grafts performed; Operation= duration of surgery; Cross-clamp=duration of aortic cross-clamping; CPB=duration of cardiopulmonary bypass; CPB temperature=minimum nasopharyngeal temperature on cardiopulmonary bypass; Time intubated= duration of tracheal intubation; ICU/HDU time=duration in intensive care unit (coronary artery bypass grafting and heart valve surgery) or high dependency unit (abdominal aortic surgery) stay; Hospital stay=duration of stay in hospital. Presented as mean (standard deviation) except * median (inter-quartile range)

	CABG	Aortic	Valve
Excluded (*n*)	6	2	0
Male (Female)	72 (14)	14 (2)	6 (8)
Age (yr)	61 (9)	69 (10)	64 (8)
Body mass index	28 (4)	27 (4)	26 (4)
Body surface area	1.9 (0.2)	1.9 (0.2)	1.8 (0.2)
Number of CABGs	3 (1)	0	0
Operation (min)	165 (37)	138 (36)	164 (46)
Cross-clamp (min)	39 (14)	57 (23)	56 (26)
CPB (min)	79 (22)	0	84 (27)
CPB Temperature (°C)	30.9 (2.0)	–	30.4 (1.5)
Time intubated (h)*	16 (9–22)	3 (2–4)	20 (14–22)
ICU/HDU time (h)*	23 (21–27)	48 (48–108)	22 (21–28)
Hospital stay (days)*	7 (7–8)	11 (9–16	8 (7–9)

In patients undergoing CABG and heart valve surgery, there were no significant effects on Sj_{O_2}or Lj by surgical operation group, time or their interaction during CPB. Over all surgical groups, Sj_{O_2} did not differ significantly between the groups (*F*=1.84, *P*=0.67, power=5%) in the postoperative period. However, there was a significant effect of time from operation upon Sj_{O_2} (*F*=22.51, *P*<0.001, power=100%) and a significant interaction between operation group and time from operation (*F*=3.45, *P*<0.001, power=98%). In the postoperative period, there were no significant effects upon Lj resulting from operation group (*F*=0.58, *P*=0.56, power=56%), time from operation (*F*=0.96, *P*=0.42, power=31%) nor because of their interaction (*F*=0.58, *P*=0.80, power=27%).

Post-hoc analysis

Post-hoc analysis found that Sj_{O_2} was decreased compared to baseline in all surgical groups on arrival on the ICU and 1 h later (Table 3). Two hours after arrival on the ICU, only the valve and abdominal aortic groups had significant decreases in Sj_{O_2} whilst 6 h after arrival, the decreases were significant only in the CABG and the abdominal aortic surgery groups. There were no significant differences in these declines between the surgical groups except 2 and 6 h after arrival on the ICU. After 2 h in the ICU, the decline in Sj_{O_2} was significantly less in patients undergoing CABG than abdominal aortic surgery whilst after 6 h in the ICU, the decline in the abdominal aortic surgery patients was significantly greater than either the CABG or valve surgery groups.

Duration of Sj_{O_2}*<50%*

Factorial analysis of variance found that the model explained little if any of the variance (adjusted r^2=0.001) in duration of Sj_{O_2}<50% (Table 5). There were no significant differences between the groups (*F*=1.65, *P*=0.20, power= 34%) nor were there any significant effects because of age

Table 2 Method comparison analysis of fibreoptic and bench measurement of jugular bulb oxyhaemoglobin saturation. CABG=coronary artery bypass grafting, CPB=cardiopulmonary bypass, bias=mean difference bench – fibreoptic oximetry, 95% CI of bias=95% confidence intervals of bias (mean difference ± t*standard error of the mean, values not including zero indicate a significant difference [*P*<0.05]), limits of agreement-mean difference ± 1.96*standard deviation

Surgery	CABG		Heart valve		Abdominal aortic	
Period	CPB	Postoperative	CPB	Postoperative	CPB	Postoperative
Patients (*n*)	84	86	14	14	–	16
Samples (*n*)	168	373	28	72	–	44
Bias [bench-fibreoptic](%)	–2.4	0.8	–2.3	0.5	–	1.2
95% CI of bias	–4.2, –0.6	0.1, 1.5	–6.2, 1.6	–1.2, 2.1	–	–0.5, 4.5
Limits of agreement (%)	–18.8, 14.1	–5.7, 7.3	–15.4, 10.8	–5.1, 6.0	–	–7.2, 11.2

Table 3 Arterial and jugular venous oxyhaemoglobin concentrations, oxygen saturation and tension, concentrations of lactate, arterial carbon dioxide tension and mean arterial pressure after induction of anaesthesia, during cardiopulmonary bypass and following coronary artery bypass grafting, abdominal aortic and heart valve surgery. Except where indicated, results are presented as mean (standard deviation) [range]. Postinduction=baseline; CPB 36°C=at 36°C during re-warming on cardiopulmonary bypass; Postop 0 h=arrival in the intensive care/high dependency unit; Postop 1 h, Postop 2 h, Postop 6 h=1, 2 and 6 h after arrival in intensive care unit (coronary artery bypass grafting and heart valve surgery) or recovery unit (abdominal aortic surgery); CABG=coronary artery bypass grafting surgery; Aortic=abdominal aortic surgery; Valve=heart valve surgery; Hba and Hbv=arterial and venous concentrations of haemoglobin; Pa_{O_2} and $P\bar{v}_{O_2}$=arterial and venous tensions of oxygen; Sa_{O_2} and Sj_{O_2}=arterial and jugular bulb saturations of oxyhaemoglobin; ΔSj_{O_2} (95% CI): change in Sj_{O_2} from postinduction presented as mean (95% confidence intervals) – values not including zero indicate a significant difference from baseline ($P<0.05$), * indicate a significant ($P<0.05$) difference compared to abdominal aortic surgery group; Pa_{CO_2}=arterial tension of carbon dioxide; MAP=mean arterial pressure; La and Lj=arterial and jugular venous concentrations of lactate

Sampling period	Operation	Hba (g dl^{-1})	Pa_{O_2} (kPa)	Sa_{O_2} (%)	Hbv (g dl^{-1})	$P\bar{v}_{O_2}$ (kPa)	Sj_{O_2}(%)
Postinduction	CABG	13.1 (1.8) [9.5–18.7]	35.3 (18.7) [8.4–72.6]	98 (2) [87–100]	13.0 (1.9) [9.0–18.8]	5.1 (1.0) [3.3–8.9]	66 (10) [46–94]
	Aortic	12.5 (1.9) [9.0–16.0]	24.0 (7.8) [12.8–41.5]	98 (2) [94–100]	12.6 (1.8) [8.5–15.7]	63 (1.7) [3.6–9.4]	74 (12) [54–91]
	Valve	12.5 (2.1) [9.2–15.8]	33.8 (14.6) [17.7–61.6]	99 (2) [95–100]	12.5 (2.1) [9.2–15.8]	5.2 (0.8) [4.2–6.7]	68 (11) 48–86
CPB 36°C	CABG	8.2 (1.3) [5.2–11.6]	44.4 (8.0) [20.4–59.8]	98 (1) [96–100]	8.2 (1.3) [5.2–11.4]	4.6 (1.1) [3.0–10.5]	59 (11) [34–96]
	Aortic	–	–	–	–	–	–
	Valve	8.4 (1.4) [6.1–11.3]	52.3 (16.6) [31.1–82.4]	98 (1) [96–99]	8.4 (1.4) [5.9–11.0]	4.6 (1.0) [3.6–7.2]	58 (10) [43–86]
Postop 0 h	CABG	9.5 (1.6) [6.8–17.7]	14.9 (5.4) [8.0–35.2]	96 (3) [84–100]	9.5 (1.6) [6.7–17.8]	4.6(1.1) [2.7–8.0]	60 (10) [41–85]
	Aortic	10.5 (1.6) [8.1–14.5]	17.1 (6.3) [10.8–27.8]	96 (4) [85–100]	10.5 (1.7) [8.0–14.6]	5.7 (1.6) [3.7–8.4]	70 (10) [53–88]
	Valve	9.7 (1.2) [7.3–12.3]	17.3 (8.3) [9.0–40.0]	96 (2) [91–98]	9.5 (1.1) [7.4–11.6]	5.0 (1.4) [3.3- 8.3]	60 (13) [43–88]
Postop 1h	CABG	9.9 (1.6) [6.9–17.1]	15.3 (4.9) [8.0–31.6]	97 (3) [79–100]	10.0 (1.6) [6.8–17.4]	4.9 (1.0) [3.2–7.4]	62 (10) [43–86]
	Aortic	10.8 (1.6) [8.1–15.1]	15.7(5.7) [8.1–27.9]	96 (4) [85–100]	10.8 (1.6) [7.9–15.4]	4.8 (0.8) [3.8–6.6]	65 (6) [56–77]
	Valve	10.4 (1.7) [7.6–13.1]	15.1 (4.8) [10.0–22.0]	96 (2) [94–99]	10.5 (1.7) [8.0–13.8]	4.4 (0.7) [2.9–5.4]	58 (9.4) 41–74
Postop 2 h	CABG	10.1 (1.6) [7.0–17.5]	16.4 (4.2) [9.4–27.2]	97 (2) [88–100]	10.2 (1.6) [6.9–18.6]	5.1 (1.0) [3.5–7.7]	65 (9) [46–88]
	Aortic	11.0 (1.7) [7.9–15.6]	15.0 (5.8) [8.1–27.9]	97 (3) [87–100]	11.0 (1.7) [7.3–15.2]	4.9 (0.9) [3.5–7.2]	66 (6) [55–73]
	Valve	10.8 (1.9) [7.7–13.4]	17.2 (4.4) [10.6–26.6]	97 (1) [95–98]	11.0 (1.8) [7.9–13.3]	4.8 (0.8) [3.2–6.7]	62 (10) [41–82]
Postop 6 h	CABG	9.3 (1.2) [7.5–15.7]	16.3 (4.2) [8.7–26.2]	97 (2) [88–100]	9.4 (1.2) [7.2–15.7]	5.1 (0.9) [3.3–7.4]	68 (8) [46–85]
	Aortic	11.9 (1.3) [9.7–14.9]	15.4 (5.5) [6.0–26.7]	96 (4) [84–100]	11.7 (1.3) [9.6–15.0]	4.5 (0.6) [3.6–5.6]	63 (7) [51–76]
	Valve	9.6 (0.9) [7.8–10.8]	15.9 (2.9) [10.8–19.8]	97 (1) [94–98]	9.7 (1.0) [7.5–11.2]	5.0 (0.9) [3.4–6.6]	69 (11) [49–86]

Sampling period	Operation	ΔSj_{O_2} (%)	n= Sj_{O_2} <50%	Pa_{O_2} (kPa)	MAP (mm Hg)	La (mmol litre^{-1})	Lj (mmol litre^{-1})
Postinduction	CABG	–	5 (6)	5.5 (0.7) [4.1–7.0]	75 (13) [49–108]	0.6 (0.2) [0.2–1.4]	0.6 (0.2) [0.3–1.1]
	Aortic	–	0 (0)	5.8 (0.7) [4.6–7.4]	81 (12) [62–100]	0.6 (0.2) [0.4–1.2]	0.6 (0.2) [0.4–1.1]
	Valve	–	1 (7)	5.7 (0.6) [4.4–6.7]	74 (15) [60–109]	0.5 (0.1) [0.4–0.8]	0.5 (0.1) [0.4–0.8]
CPB 36°C	CABG	–	11 (13)	4.4 (0.6) [3.2–6.2]	61 (13) [32–96]	1.8 (0.5) [0.9–3.1]	1.7 (0.5) [0.8–3.3]
	Aortic	–	–	–		–	–
	Valve	–	2 (14)	4.2 (0.6) [3.3–5.3]	61 (12) [42–81]	1.4 (0.4) [0.9–2.1]	1.3 (0.5) [0.6–2.3]
Postop 0 h	CABG	–6 [–9, –4]	16 (19)	5.4 (0.8) [3.8–8.1]	78 (14) [52–124]	1.5 (0.6) [0.5–3.5]	1.5 (0.6) [0.5–3.3]
	Aortic	–4 [–9, 1]	0 (0)	6.4 (1.2) [5.0–9.9]	83 (18) [60–116]	1.0 (0.4) [0.6–2.0]	1.0 (0.4) [0.6–2.0]
	Valve	–8 [–13, –2]	2 (14)	5.5 (0.9) [4.2–7.6]	82 (11) [64–104]	1.2 (0.4) [0.6–2.1]	1.1 (0.4) [0.6–2.0]
Postop 1h	CABG	–4 [–6, –1]	8 (9)	5.7 (0.9) [4.1–7.6]	84 (15) [54–131]	1.5 (0.7) [0.4–4.0]	1.5 (0.7) [0.4–3.9]
	Aortic	–9 [–16, –3]	0 (0)	6.0 (0.9) [4.8–7.9]	86 (18) [53–123]	0.7 (0.3) [0.4–1.3]	0.8 (0.3) [0.4–1.3]
	Valve	–10 [–16, –5]	2 (14)	5.2 (0.8) [3.6–7.0]	88 (13) [63–113]	1.1 (0.5) [0.5–2.0]	1.1 (0.5) [0.6–2.0]
Postop 2 h	CABG	–1 [–4, 2]*	1 (1)	5.8 (0.8) [4.2–7.6]	84 (14) [55–129]	1.5 (0.9) [0.4–5.5]	1.5 (0.8) [0.4–5.2]
	Aortic	–8 [–14, –2]	0 (0)	5.7 (0.8) [4.4–6.7]	87 (15) [57–22]	0.7 (0.2) [0.4–1.3]	0.7 (0.2) [0.4–1.3]
	Valve	–6 [–11, –0]	1 (7)	5.3 (0.6) [4.2–5.9]	87(12) [65–108]	1.1 (0.6) [0.6–2.3]	1.1 (0.6) [0.6–2.2]
Postop 6 h	CABG	2 [+0, 4]*	1 (1)	5.8 (0.8) [4.1–8.1]	73 (13) [46–137]	1.7 (1.4) [0.4–8.4]	1.7 (1.4) [0.3–8.1]
	Aortic	–11 [–17, –5]	0 (0)	5.5 (0.8) [4.4–6.8]	83 (16) [54–109]	0.7 (0.3) [0.4–1.4]	0.7 (0.3) [0.4–1.4]
	Valve	1 [–7, 8]*	2 (14)	5.4 (0.8) [4.4–7.6]	76 (11) [57–96]	1.2 (0.9) [0.5–3.4]	1.2 (0.9) [0.6–3.3]

(B=0.02, P=0.52), CPB time (B=0.01, P=0.34) nor time until tracheal extubation (B=–0.076, P=0.75).

Discussion

The present study confirms the findings of our initial observation, preliminary report and subsequent work that $Sj_{O_2}<50\%$ occurs in many patients in the early postoperative period following CABG surgery.[2 9 13] Further, it indicates that $Sj_{O_2}<50\%$ is also a phenomenon of heart valve surgery. What is less clear is whether $Sj_{O_2}<50\%$ also occurs following abdominal aortic surgery as the findings from fibreoptic and bench oximetry are conflicting. Our assumption that $Sj_{O_2}<50\%$ only happens following cardiac surgery was ill founded as patients having abdominal aortic surgery had a similar duration of $Sj_{O_2}<50\%$ when using fibreoptic measurements. However, the analysis indicates our study has only a limited statistical power to exclude the possibility that there are small but true differences in the duration of $Sj_{O_2}<50\%$ between the groups.

In contrast to the fibreoptic method, bench oximetry measurements of discrete jugular bulb blood samples found

Table 4 Covariates included in the repeated measures analysis of variance. Sj_{O_2}=oxygen saturation of jugular bulb haemoglobin; Lj=jugular bulb concentration of lactate; Pa_{CO_2}=arterial tension of carbon dioxide; La=arterial concentration of lactate; MAP: mean arterial pressure; Hba=arterial concentration of haemoglobin; Sa_{O_2}=oxygen saturation of arterial haemoglobin; CPB time=duration of cardiopulmonary bypass; B=regression coefficient; Beta=Beta coefficient (standardized Z-score form)

	Cardiopulmonary bypass			**Postoperative**		
Covariate	**B**	**Beta**	***P***	**B**	**Beta**	***P***
Dependent variable: Sj_{O_2}						
Pa_{CO_2} (kPa)	4.146	0.257	0.016	9.358	0.759	<0.001
La (mmol l^{-1})	1.420	0.058	0.587	1.559	0.140	0.068
MAP (mm Hg)	0.043	0.048	0.650	0.078	0.110	0.143
Hba (g dl^{-1})	−0.338	−0.063	0.581	−0.619	−0.115	0.133
Sa_{O_2} (%)	0.300	0.046	0.672	0.510	0.129	0.090
Age (yr)	−0.060	−0.068	0.525	−0.051	−0.066	0.342
CPB time (min)	−0.017	−0.050	0.625	0.008	0.038	0.724
Dependent variable: Lj						
Pa_{CO_2} (kPa)	−0.023	−0.035	0.284	0.009	0.008	0.216
La (mmol $litre^{-1}$)	0.929	0.939	0.000	0.959	1.002	<0.001
MAP (mm Hg)	0.000	−0.001	0.983	0.001	0.011	0.127
Hba (g $litre^{-1}$)	−0.008	−0.035	0.324	−0.006	−0.013	0.058
Sa_{O_2} (%)	0.007	0.028	0.401	0.000	0.001	0.866
Age (yr)	−0.001	−0.023	0.499	0.000	0.002	0.710
CPB time (min)	0.000	−0.002	0.943	0.000	0.002	0.830

that no patients undergoing abdominal aortic surgery experienced Sj_{O_2}<50%. This difference may be because fibreoptic measurements of Sj_{O_2}<50% occurred at times other than when blood samplings were performed as all discrete measurements of Sj_{O_2} were greater than 50% in patients having abdominal aortic surgery. Indeed, inspection of the data logs of patients having abdominal aortic surgery found that most of the episodes of Sj_{O_2}<50% occurred between 6 and 18 h surgery. In contrast, when using discrete sampling, most of the episodes of Sj_{O_2}<50% occurred within 6 h in patients having heart surgery. As measurements were only compared for 6 h after arrival in the ICU, it cannot be excluded that fibreoptic measurements of Sj_{O_2}<50% beyond this time were artefactual. This may have arisen because tracheal extubation was performed earlier in patients having abdominal aortic surgery than in those having cardiac surgery. Patients having abdominal aortic surgery may therefore have been more likely to move and so cause the fibreoptic catheter to give artefactual signals when it impinged on the wall of the jugular bulb. However, this hypothesis is not supported by the lack of correlation between the time to tracheal extubation and duration of Sj_{O_2}<50%.

Although none of the patients undergoing abdominal aortic surgery experienced Sj_{O_2}<50% when discrete blood sampling and bench oximetry was used, they did have the highest mean decreases in Sj_{O_2} compared to baseline. This fits with the baseline values of Sj_{O_2} following induction of anaesthesia being higher, and postoperative values being lower, in patients undergoing abdominal vascular surgery than those having either the CABG or heart valve surgery. Thus, there are between group differences in both baseline values and changes in Sj_{O_2} following surgery that require explanation.

One possible explanation is that these differences were the result of differences in MAP.[11 12] However, unlike the studies of Yoshitake and colleagues and Grubenhofer and colleagues, we found no significant correlation between MAP and Sj_{O_2} during CPB.[11 12] In addition, we also found no significant correlation between Sj_{O_2} and MAP in the early postoperative period. This latter finding is supported by cerebral blood flow studies undertaken by McNeill and colleagues, which found cerebral autoregulation to be maintained at this time.[18]

In the present study, Pa_{CO_2} had an extremely important influence on Sj_{O_2}, both during CPB and after surgery. This has been reported by Yoshitake and colleagues during CPB and by us, following surgery.[9 11] Again, this is supported by McNeill and colleagues' study which found that cerebral blood flow is highly influenced by Pa_{CO_2}.[18] For this reason, although there was a marked decrement in Sj_{O_2} from baseline on CPB, it was not statistically significant after correction for the concomitant decrease Pa_{CO_2}. Similarly, the changes in Pa_{CO_2} from baseline varied between surgical groups, most likely as a result of differences in ventilatory management, and this variance influenced the changes in Sj_{O_2} that occurred between the groups. Variance in Pa_{CO_2} between groups may explain why, when using discrete measurements, Sj_{O_2}<50% was a phenomenon of cardiac but not abdominal aortic surgery.

Notwithstanding the important influence of Pa_{CO_2}, the significant effect upon Sj_{O_2} resulting from the interaction between time from surgery and surgical group remains unexplained. Differences in anaesthetic technique could have played a part as Nandate and colleagues have found that the choice of anaesthetic agent influences Sj_{O_2} not only during CPB, but also after heart surgery.[19] However, this study cannot exclude the possibility that changes in Sj_{O_2}

Table 5 Duration of jugular bulb oxyhaemoglobin desaturation. CABG=coronary artery bypass grafting surgery; Aortic=abdominal aortic surgery; Valve=heart valve surgery; Monitoring=duration monitored; $Sj_{O_2}<50\%$: duration that the saturation of jugular bulb was less than 50% (minutes); Percentage=percentage of monitored time with $Sj_{O_2}<50\%$; Per 25 and Per 75=25th and 75th percentiles

Operation	n		Mean	SD	Median	Per 25	Per 75
CABG	86	Monitoring	1054	82	1079	1070	1080
		$Sj_{O_2}<50\%$	67	87	37	0	102
		Percentage	7	9	4	0	10
Aortic	16	Monitoring	893	259	1018	788	1061
		$Sj_{O_2}<50\%$	113	100	100	16	191
		Percentage	13	12	11	1	22
Valve	14	Monitoring	1073	40	1080	1065	1080
		$Sj_{O_2}<50\%$	91	180	15	0	139
		Percentage	8	17	1	0	14

following surgery are the result of pathological processes such as cerebral oedema or increased cerebrovascular resistance.[20 21]

Visual inspection of the Lj data suggests that patients having abdominal aortic surgery have lower Ljs than those undergoing cardiac surgery. This difference between operative groups, as well as that within patients, is explained by the positive correlation between Lj and the concentration of arterial lactate. Unlike patients undergoing abdominal aortic surgery, those having CPB will have received a large quantity of lactate from the lactated Ringer's solution in the crystalloid prime for the CPB pump. However, repeated measures MANOVA, which having first corrected for the concentration of arterial lactate, found no significant effects on Lj. This implies that patients did not experience cerebral ischaemia as this would have increased cerebral lactate production.

The lack of reciprocation between levels of Sj_{O_2} and Lj indicates that $Sj_{O_2}<50\%$ may not be a valuable estimate of cerebral ischaemia in this setting. Rather, $Sj_{O_2}<50\%$ appears to be largely caused by hypocapnia inducing cerebral vasoconstriction. This in turn decreases cerebral blood flow and any decrement in cerebral oxygen delivery is compensated for by increased oxygen extraction. Therefore, $Sj_{O_2}<50\%$ in the early postoperative period may not be an important cause of cerebral injury that is associated with heart surgery. Indeed, the findings of the present study explain why, in work undertaken after the present study, we were unable to find an important relationship between either the duration of $Sj_{O_2}<50\%$ or Lj and cognitive outcome three months after CABG surgery.[13] Future studies investigating brain damage associated with CABG surgery should therefore consider causal factors other than postoperative $Sj_{O_2}<50\%$.

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References

1 Alston RP, Souter MJ. Cerebral sequelae of cardiac surgery. *Curr Opinion Crit Care* 2000; **6**: 92–7

2 Souter MJ, Andrews PJD, Alston RP. Jugular venous desaturation following cardiac surgery. *Br J Anaesth* 1998; **81**: 239–41

3 Croughwell ND, Newman MF, Blumenthal JA *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58**: 1702–8

4 Andrews PJD, Colqhuhoun AD. Detection of cerebral hypoperfusion during cardiopulmonary bypass. *Anaesthesia* 1994; **49**: 949–53

5 Nakajima T, Kuro M, Hayashi Y, Kitaguchi K, Uchida O, Takaki O. Clinical evaluation of cerebral oxygen balance during cardiopulmonary bypass: On-line continuous monitoring of jugular venous oxyhemoglobin saturation. *Anesth Analg* 1992; **74**: 630–5

6 Souter MJ, Andrews PJD, Alston RP. Propofol does not ameliorate cerebral venous oxyhemoglobin desaturation during hypothermic cardiopulmonary bypass. *Anesth Analg* 1998; **86**: 926–31

7 Robertson CS, Gopinath RK, Goodman JC, Contant CF, Valadka AB, Narayan RK. $SjVO_2$ monitoring in head-injured patients. *J Neurotrauma* 1995; **12**: 891–6

8 Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg* 1992; **76**: 212–17

9 Millar SA, Alston RP, Souter MJ, Andrews PJD. Aerobic, anaerobic and combination estimates of cerebral hypoperfusion during and after cardiac surgery. *Br J Anaesth* 1999; **81**: 936–9

10 Sapire KJ, Gopinath SP, Thakar DR, Gabrielli A, Jones JW, Robertson CS. Cerebral oxygenation during warming after cardiopulmonary bypass. *Crit Care Med* 1997; **25**: 1655–62

11 Yoshitake A, Goto T, Baba T, Shibata Y. Analysis of factors related to jugular venous oxygen saturation during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1999; **13**: 160–4

12 Grubhofer G, Lassnigg AM, Schneider B, Rajek MA, Pernerstorfer T, Hiesmayr MJ. Jugular venous bulb oxygen saturation depends on blood pressure during cardiopulmonary bypass. *Ann Thorac Surg* 1998; **65**: 653–8

13 Robson MJ, Alston RP, Deary IJ, Andrews PJD, Souter MJ, Yates S. Cognition after coronary artery surgery is not related to postoperative jugular bulb desaturation. *Anesth Analg* 2000; **91**: 1317–26

14 Walsh TS, Lee A. Mathematical coupling in medical research: lessons from studies of oxygen kinetics. *Br J Anaesth* 1998; **81**: 118–20

15 Norusis MJ. *SPSS Advanced Statistics 6.1*. Chicago: Prentice Hall, 1994

16 Millar SA, Alston RP, Souter MJ, Andrews PJD. Continuous monitoring of jugular bulb oxyhaemoglobin saturation using the Edslab dual lumen oximetry catheter during and after cardiac surgery. *Br J Anaesth* 1999; **82**: 521–4

17 Gopinath SP, Robertson CS, Contant CF *et al.* Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psychiatr* 1994; **57**: 717–23

18 McNeill BR, Murkin JM, Farrar JK, Gelb AW. Autoregulation and the CO_2 responsiveness of cerebral blood flow after cardiopulmonary bypass. *Can J Anaesth* 1990; **37**: 313–7

19 Nandate K, Vuylsteke A, Ratsep I *et al.* Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery. *Br J Anaesth* 2000; **84**: 631–3

20 Harris DNF, Bailey SM, Smith PLC, Taylor KM, Oatridge A, Bydder GM. Brain swelling in first hour following coronary artery bypass surgery. *Lancet* 1993; **342**: 586–7

21 Prough DS, Rogers AT, Stump DA *et al.* Cerebral blood flow decreases with time whereas cerebral oxygen consumption remains stable during hypothermic cardiopulmonary bypass in humans. *Anesth Analg* 1991; **72**: 161–8

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Do physiological changes in pregnancy change defibrillation energy requirements?

J. Nanson*, D. Elcock, M. Williams and C. D. Deakin

Shackleton Department of Anaesthesia, Southampton University Hospitals NHS Trust, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK

**Corresponding author*

Resuscitation during pregnancy is uncommon, with approximately 70 deaths occurring during pregancy in the UK per annum. Physiological changes during pregnancy may affect transthoracic impedance (TTI), which determines transmyocardial current. Increased blood volume, cardiomegaly, haemodilution, changes in lung volume and changes in thoracic volume may alter impedance in ways that are difficult to predict. We measured TTI at term and after delivery once physiological changes had resolved. Mean (SD) TTI was 91.3 (15.8) Ω at term and 91.6 (11.8) Ω 6–8 weeks after delivery; the difference was not statistically significant. We conclude that current energy requirements for adult defibrillation are appropriate for use during pregnancy.

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Keywords: measurement techniques, transthoracic impedance; pregnancy; heart, defibrillation

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Deaths in pregnancy are relatively rare but have a particularly significant impact in terms of the young age of the mother, the mortality of the unborn child and the long-term effects on the family. In the UK, deaths during pregnancy exceed 70 per annum.[1]

Resuscitation may involve defibrillation for treatment of ventricular arrhythmias. The transthoracic current generated during defibrillation must depolarize a critical mass of myocardium to achieve successful reversion to sinus rhythm. Transmyocardial current is only about 4% of the total transthoracic current,[2] so any factors that reduce transthoracic current may reduce transmyocardial current with an adverse effect on the success of defibrillation.

Physiological changes during pregnancy may change transthoracic impedance (TTI) and therefore affect transthoracic current during defibrillation. Increased intra- and extracellular fluid, increased blood volume, structural changes in the heart,[3–6] changes in functional residual capacity of the lungs and increased thoracic volume may all change TTI and current pathways with unpredictable results.

We examined TTI at term and 6–8 weeks after delivery, once pregnancy-related physiological changes had resolved, to establish whether changes in TTI could affect defibrillation energy requirements at term.

Materials and methods

Following Ethics Committee approval and written informed consent, we sequentially recruited 45 women with uncomplicated pregnancy within 2 weeks of estimated date of delivery who were attending the Princess Anne Hospital, Southampton. TTI was measured before delivery and 6–8 weeks after delivery.

TTI was measured using MultiScan 5000 impedance-measuring equipment (Bodystat Ltd, Isle of Man, UK). Self-adhesive defibrillation pads (Hewlett Packard M1749B) were placed according to the current guidelines of the European Resuscitation Council in an anterior-apical position.[7] We avoided placing the apical pad over the breast. Impedance was measured using a low-current monophasic wave at 30 kHz averaged over a 3 s period. The subjects felt no electrical current or pain during measurements. This technique measures total transthoracic impedance as 'seen' by the defibrillator (impedance of skin–electrode interface plus impedance of intrathoracic pathways). Three TTI

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Table 1 Patient characteristics

	Mean	Range
Age (years)	32	19–42
Height (cm)	162.4	147.0–175.0
Weight (kg)		
at term	81.6	54.0–115.0
after delivery	70.5	47.0–97.0
Body mass index (kg m^{-2})		
at term	30.9	20.3–42.5
after delivery	26.7	18.1–38.3

measurements were made at end-expiration while breath was held for the duration of the measurement and the average measurement was recorded. All measurements were made with the subject reclining at 45° to the horizontal.

Statistical analysis

Calculation of sample size for paired data requires an estimate of the SD of the difference between measurements. We had no data on which to base estimates but assumed that 1 SD of the difference would be no greater than the SD of TTI of a population of normal subjects, which we know from previous studies to be approximately 7 Ω in a similar age group.[8] We estimated, therefore, that to detect a difference of >10% change in TTI, assuming a baseline TTI of approximately 66 Ω as found with previous studies,[8] a total of 40 patients would be required for the study to give a power >0.80 at $P<0.05$.[9] TTI is know to have a parametric distribution and results were analysed using a paired two-way *t*-test. Significance was taken as $P<0.05$.

Results

Forty-five women consented to measurement of TTI at term. *Post partum* measurements were made 6–8 weeks later on 42 of these women; the remaining three patients declined to be measured for a second time. Patient characteristics are given in Table 1. The mean (SD) TTI was 91.3 (15.8) Ω at term (range 63.0–137.7 Ω) and 91.6 (11.5) 6–8 weeks after delivery (range 69.3–118.3 Ω). There was no statistically significant difference between the two groups ($P>0.80$).

Examining for a 10% difference in TTI between the two groups, the standardized difference[9] was 0.64, giving the study a power of >0.80 at $P<0.05$.

Discussion

Cardiac arrest during pregnancy is a rare event: <1% of deaths in the female population aged 15–44 yr occur during pregnancy. In the UK, this equates to approximately 70 direct and indirect deaths per annum.[1] The proportion of these cases requiring defibrillation for ventricular arrhythmias is unknown. Pulseless electrical activity (PEA) is likely to be a common presenting arrhythmia in deaths from pulmonary embolism, hypovolaemia and amniotic fluid embolus but may often degenerate to ventricular fibrillation.

Physiological changes during pregnancy may affect TTI and, therefore, transthoracic current during defibrillation. During normal pregnancy, total body water increases by 6–8 litres, of which 4–6 litres is extracellular and at least 2–3 litres interstitial.[3] A 40–50% increase in blood volume occurs, most of which is in the venous system and increases thoracic blood volume and pulmonary blood volume. The heart remodels early, and by term has increased in end-diastolic volume[6] and undergone mild ventricular hypertrophy and dilation.[5] Reduced plasma oncotic pressure may increase the water content of the lungs.[4] These factors may decrease TTI by improving electrical conductivity through the tissues. Conversely, increased thoracic volume may increase TTI by increasing current pathways between paddles. Overall, the effects on TTI are difficult to predict.

Physiological changes resolve rapidly after delivery. Most changes in blood volume and fluid shifts have returned to normal by 2 weeks.[5] We assumed that the physiological state would have returned to that of a non-pregnant woman by 6–8 weeks after delivery. Although resolution of mild ventricular hypertrophy seen at term takes ≥5 months,[10] we considered that 6–8 weeks after delivery, its effects on overall TTI would be negligible.

We found no significant change in TTI during pregnancy, and so conclude that current guidelines for energy requirements for adults are appropriate for use during pregnancy. Although an unchanged TTI does not necessarily mean that current pathways and, in particular, transmyocardial current, are unchanged, we believe that transmyocardial current is unlikely to be altered significantly if overall TTI is unchanged.

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References

1 Department of Health. *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–6.* London: HMSO, 1998

2 Bossaert L, Koster R. Defibrillation: methods and strategies. *Resuscitation* 1992; **24**: 211–225

3 Davison JM. Edema in pregnancy. *Kidney Int* 1997; **51**: S90–96

4 Hytten F. Blood volume changes in normal pregnancy. *Clin Haematol* 1985; **14**: 601–12

5 Hunter S, Robson S. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; **68**: 540–3

6 Thornberg KL, Jacobson SL, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. *Semin Perinatol* 2000; **24**: 11–14

7 Advanced Life Support Working Group of the ERC. Guidelines for advanced life support. *Resuscitation* 1992; **24**: 111–132

8 Deakin CD, McLaren RM, Petley G, Dalrymple-Hay M, Clewlow F. Effects of positive end-expiratory pressure on transthoracic impedance—implications for defibrillation. *Resuscitation* 1998; **37**: 9–12

9 Altman D. Statistics and ethics in medical research: how large a sample? *Br Med J* 1980; **281**: 1336–8

10 Duvekot J, Peeters L. Maternal cardiovascular haemodynamic adaptation to pregnancy. *Obstet Gynecol Surv* 1994; **49**: S1–14

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Homozygous and heterozygous Arg614Cys mutations (1840C→T) in the ryanodine receptor gene co-segregate with malignant hyperthermia susceptibility in a German family

H. Rueffert[1]*, D. Olthoff[1], C. Deutrich[1], B. Thamm[1] and U. G. Froster[2]

[1]Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Liebigstr. 20a, D-04103 Leipzig, Germany. [2]Institute for Human Genetics, University of Leipzig, Philipp-Rosenthal-Str. 55, D-04103 Leipzig, Germany

**Corresponding author*

The determination of susceptibility to malignant hyperthermia (MH) by genetic investigation is a controversial issue because of the genetic heterogeneity of this disorder. The requirement for such an approach in MH diagnosis is a strong correlation between MH-associated genetic abnormalities and phenotypic findings in the *in vitro* contracture test (IVCT). After a severe clinical MH crisis during general anaesthesia a patient was diagnosed by the IVCT in which susceptibility to MH was confirmed. Genetic screening for MH-related mutations in the RYR1 gene revealed the presence of a homozygous 1840C→T base exchange (Arg614Cys substitution) in this patient. A specific search for this defect in 20 relatives led to the identification of a total of 11 Arg614Cys mutations. Of these, 10 were heterozygous (including both parents) and one was homozygous (sister). Further IVCTs were subsequently performed on the parents of the index patient, the homozygous sister and all relatives who did not carry the Arg614Cys in order to determine the genotype/phenotype correlation. After analysing these data, and because of the strong correlation between clinical, phenotypic, and genetic results in the index patient, we assigned the diagnosis 'MHS' to all the remaining Arg614Cys mutation carriers of that family without performing the IVCT.

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Malignant hyperthermia (MH) is an inherited autosomal-dominant disorder in which halogenated inhalational anaesthetics and depolarizing neuromuscular blocking drugs may trigger a life-threatening increase of muscle metabolism in susceptible individuals.[1] MH may occur in any age group. The typical severe MH crisis is characterized by masseter spasm, generalized muscle rigidity, tachycardia, hypercapnia, cyanosis, high fever, and mixed acidosis. The clinical signs of this hypermetabolic syndrome are caused by an increased concentration of free myoplasmic calcium. However, an MH episode may also be associated with slight, non-specific, ambiguous symptoms which can make the diagnosis difficult and possibly delay therapeutic intervention.[2–4] To complicate matters, MH symptoms may also occur after repeated trouble-free general anaesthesia with triggering agents. Nevertheless, the outcome for the patient depends on the severity of the clinical presentation of MH, and this in turn depends on early diagnosis and initiation of treatment.

The MH disposition in suspected individuals or families may be determined by *in vitro* contracture testing (IVCT) of a skeletal muscle biopsy; this is at present felt to be the most reliable diagnostic method. The procedures for IVCT were developed by the European and North American malignant hyperthermia groups (EMHG, NAMHG). They show a high sensitivity (99% for EMHG, 92–97% for NAMHG) and specificity (94% for EMHG, 53–78% for NAMHG).[5–7] Besides determining MH disposition, the IVCT is the basic requirement for interpreting genetic MH data.

An important step towards understanding the pathogenesis of the disease was the identification of MH-associated genetic mutations. The ryanodine receptor (RYR1), which represents the calcium release channel of skeletal muscle sarcoplasmic reticulum, was considered to

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be the primary locus for MH susceptibility.[8–10] In approximately 50% of MH families, a link with the coding region of the RYR1 gene (MHS1 locus on chromosome 19q12–13.1) can be detected.[11] Over 20 point mutations in the RYR1 gene have so far been found to segregate with the MHS phenotype.[12] For most of these missense mutations it has been possible to identify functional effects on the calcium channel reflecting an increased sensitivity of calcium release to triggering substances.[13] Because of this established genotype/phenotype correlation, carriers of a known MH-related mutation should be regarded as having a high risk of MH.[13–15] A genetic MH analysis may, therefore, be useful for family screening. Guidelines for molecular genetic work have recently been compiled by the EMHG.[16] Using a family with a predisposition to MH as an example, we shall now discuss the diagnostic approaches currently available for determining the MH disposition.

Patients and methods

Patients

The MH family was identified through a 43-yr-old index patient who developed typical symptoms of a severe MH crisis during general anaesthesia for an appendectomy. Anaesthesia was induced with thiopental, in a dose sufficient to abolish the eyelash reflex (400 mg i.v.). Alfentanil (1.5 mg i.v.) and succinylcholine (100 mg i.v.) were given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with 0.6–1.0% halothane and 60% nitrous oxide in oxygen. Five minutes after the induction of anaesthesia, the patient developed a tachycardia of 160 beats min^{-1}; the end-tidal concentration of carbon dioxide subsequently rose rapidly to 9.33 kPa and the body temperature to 39.6°C so that the patient was immediately suspected of developing MH. Standard treatment for an acute MH reaction, including the use of dantrolene, was successful In the post-operative period the serum creatine kinase concentration reached 22 000 IU litre^{-1}.

Three months after this incident the patient underwent the IVCT.

In vitro contracture test

The IVCT was performed according to the criteria of the standard procedure of the European MH group.[5] The test determines the threshold concentrations of halothane and caffeine that produce a contracture force ⩾2 mN in an isolated muscle specimen. Depending on the results, the tested individual is classified as MH susceptible (MHS). MHS: contracture force ⩾2 mN at a caffeine concentration of 2.0 mmol litre^{-1} or less and a halothane concentration of 0.44 mmol litre^{-1} or less; MH negative (MHN): contracture force ⩾2 mN at a caffeine concentration of 3.0 mmol litre^{-1} or more and a halothane concentration greater than 0.44 mmol litre^{-1}; or MH equivocal (MHE): contracture force ⩾2 mN at a caffeine concentration of 2.0 mmol litre^{-1} or less (MHEc) or a halothane concentration of 0.44 mmol litre^{-1} or less (MHEh).

Molecular genetic investigation

Direct sequencing

Genomic DNA was prepared from whole blood. The index patient was screened for published MH-related mutations in the amino terminal and central region of the RYR1 gene by PCR amplification and direct sequencing. Purified PCR products were directly sequenced by the ABI Prism DNA Sequencing Kit (Perkin Elmer, USA). The samples were then loaded on 5.25% PAGE-PLUS gel (Amresco), electrophoresed in the ABI PRISM 377 Sequencer (Perkin Elmer) and aligned with Sequence Navigator Software (Perkin Elmer). Both strands were sequenced and compared to permit identification of ambiguities.

Restriction enzyme analysis

A 918-bp[17] PCR product of RYR1 exon 17 was digested with the restriction enzyme *Rsa*I. Standard PCR conditions were used for amplification: denaturation at 95°C for 1 min, annealing at 62°C for 1 min, extension at 72°C for 2 min, 30 cycles; forward primer 5′-TTG CCA CAT CTT ATC CCG ATG CGC; reverse primer 5′-GAA CCT GTC CAG AGA TGC AGT CCA TC. After purification, the PCR product was mixed with 10 U of the restriction enzyme *Rsa*I and incubated for 8 h at 37°C. According to GenBank (Accession no.: U48557) the following fragments were to be expected (OMIGA 1.1, Oxford Molecular Ltd.): normal type 166, 553, 12, 185, 2 bp; heterozygous C1840T-mutation 166, 553, 719, 12, 185, 2 bp; homozygous C1840T-mutation 719, 185, 12, 2 bp. A 719-bp fragment occurred because of the loss of one restriction site (553+166 bp).

Results

When the index patient's symptoms were rated on the clinical grading scale[18] for MH the likelihood of MH was found to be very high indeed (raw score range: 50+; MH rank: 6). The clinical MH diagnosis was confirmed by the results of the IVCT in which the patient showed low threshold concentrations and high contracture forces for halothane and caffeine (Table 1, II:3). The molecular genetic search for the most frequent MH-related mutations by the direct sequencing technique revealed the presence of a base exchange from C to T at position 1840 of the RYR1 gene (replacement of Arg614 by Cys), surprisingly in a homozygous state.

All the relatives were then screened specifically for the Arg614Cys mutation by restriction enzyme analysis (Fig. 1). As expected, both parents (I:1, I:2) were heterozygous carriers of the mutation. The mutation was also detected in

Table 1 Results of genotyping (search for the MH-related mutation Arg614Cys) and phenotyping (*in vitro* contracture test) of individuals for whom both diagnostic methods were used

Individual	**Threshold concentration**		**Contracture force (mN)**		**Diagnosis**	**Arg614Cys mutation**
	Halothane mmol litre^{-1}	**Caffeine mmol litre^{-1}**	**Halothane 2 vol%**	**Caffeine mmol litre^{-1}**		
I:1	0.44	2.0	5.5	5	MHS	Heterozygous
I:2	0.22	2.0	15	3.5	MHS	Heterozygous
II:3	0.11	0.5	23.5	23	MHS	Homozygous
II:9	0.11	0.5	21	19	MHS	Homozygous
II:10	0.66	3.0	1	1	MHN	None
II:12	>0.66	>4	0	0	MHN	None
III:1	>0.66	>4	1	0	MHN	None
III:2	>0.66	>4	0	0	MHN	None
III:4	>0.66	>4	1	0	MHN	None
III:5	>0.66	>4	0	0.5	MHN	None

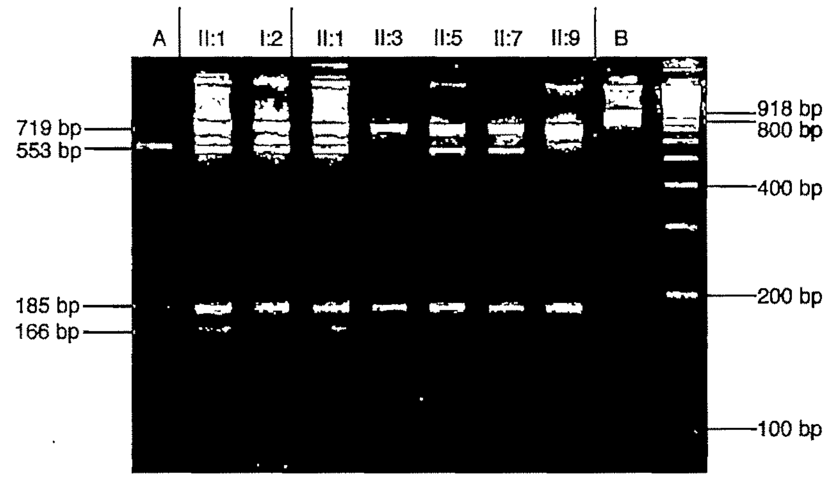

Fig 1 Restriction enzyme analysis. The identification of the Arg614Cys mutation is represented by the appearance of the 719-bp fragment in the gel electrophoresis. The index patient (II:3) and his sister (II:9) are homozygous for this mutation (loss of the 166-bp fragment). The parents and the remaining siblings are heterozygous carriers. Band A indicates the normal type, band B the undigested 918-bp sequence of the RYR 1 gene. The 12 bp and 2 bp fragments are not visible.

all the siblings of the index patient. A further homozygous base exchange was found in one sister (II:9), and her children were necessarily affected by this mutation too (III:7, III:8). The molecular genetic results for the whole family are shown in Figure 1. Out of 21 individuals examined genetically, the Arg614Cys mutation was detected in 12; of these, 10 were heterozygous and two were homozygous. The presence of two homozygous Arg614Cys mutations within one family is an extremely rare finding.

According to the EMHG guidelines,[16] those family members who did not carry the mutation observed in the pedigree had to undergo the IVCT investigation. As Table 1 shows, it was possible to exclude a positive MH disposition with certainty for these individuals because of the MHN diagnosis in the IVCT. Moreover, no discordance between the IVCT and the genetic investigation was observed in either MHS or MHN individuals.

An additional IVCT investigation was carried out on the homozygous sister and both heterozygous parents of the index patient as it seemed useful to compare threshold concentrations and contracture forces of these different genotypes. As expected, the homozygous individuals showed significantly lower threshold concentrations and noticeably higher contracture forces for the two triggering substances halothane and caffeine (Table 1).

Discussion

The role of the RYR1 gene in MH has been confirmed by the discovery of numerous RYR1 missense mutations in MH families. More than 20 mutations have so far been identified as segregating with the MHS trait; most mutation carriers are heterozygous.[12] MHS homozygotes are considered rare in the affected MH population. Only two MHS homozygotes have been detected for the Cys35Arg and one for the Arg614Cys mutation.[19 20]

The Arg614Cys mutation was the first human mutation found to be associated with MH.[8] The majority of patients

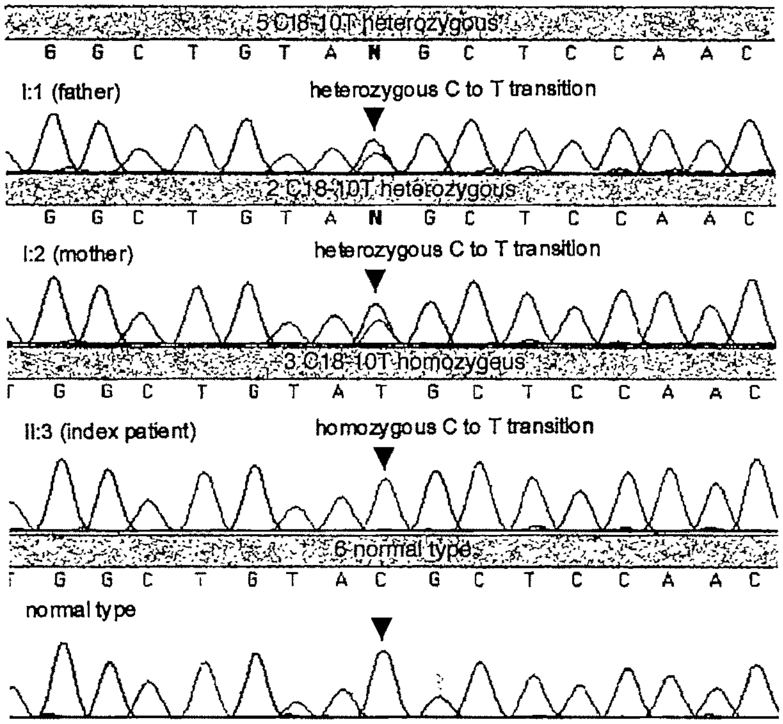

Fig 2 Sequencing of the gene segment for the ryanodine receptor with the suspected Arg614Cys (1840C→T) mutation. A complete C to T transition in both alleles (homozygous inheritance) was identified in the index patient; the parents carried the mutation in a heterozygous state.

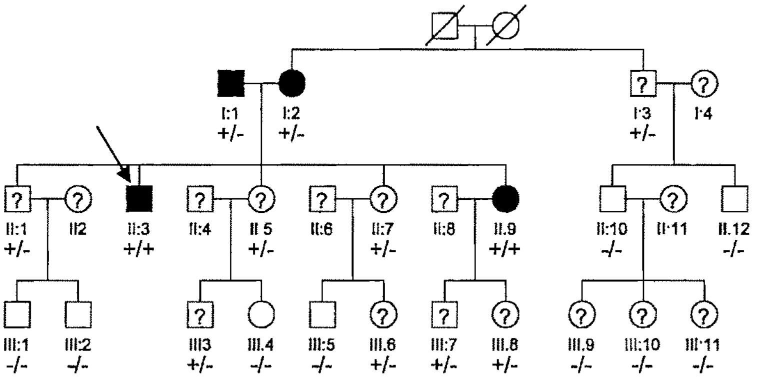

Fig 3 Prevalence of the RYR1 mutation Arg614Cys in the MH family investigated. The figure shows the results of molecular genetic screening and IVCT. Filled symbols denote persons tested with the IVCT and typed as MHS, opened symbols denote persons tested and typed as MHN, open symbols with question mark denote untested family members. Genotype: +/+, homozygous mutation carrier; +/–, heterozygous mutation carrier; –/–, absence of the mutation. Individual II:3 (arrow) is the index patient who had a MH event.

carrying this mutation were classified as MH-susceptible in the IVCT. However, some cases of discordance between the genotype and the phenotype were described for the Arg614Cys mutation, and this raised doubts as to whether the mutation is really the cause.[20 21] Most doubts concerned discrepancies between MHS results in the IVCT and the absence of the mutation. Attempts were made to explain these findings by implicating further independent unknown mutations, which might cause MH; therefore, suggesting that the single-gene model underlying MH may be incorrect. This interpretation was reinforced by the identification of five additional MH loci on chromosomes 17q,7q, 3q, 1q, and 5p22-25.

On the other hand, an explanation for the occurrence of genotype/phenotype discordance may lie in the IVCT, which does not guarantee total phenotypic accuracy. According to the EMHG procedure the IVCT has a sensitivity of 99% and a specificity of 94%.[6] Moreover, a recent study shows a considerable between-centre variability of the IVCT results for the same patient.[26]

The study described here is an excellent example of the effects of the Arg614Cys mutation on the MH phenotype.

A strong correlation between clinical, IVCT and molecular genetic findings was first established for the homozygous index patient who had developed an MH crisis. Furthermore, both the homozygous sister (II:9) and the heterozygous parents (I:1, I:2) were diagnosed as MHS in the IVCT. The two homozygous individuals showed much greater contracture responses to both halothane and caffeine than the heterozygous subjects. The absence of the Arg614Cys mutation in all MHN individuals also supports the strong association of the mutations with susceptibility. No genotype/phenotype discordance was observed for MHS or MHN individuals.

These results support previous assumptions that inheritance of homozygous-dominant alleles is associated with a more severe phenotype possibly arising from a more deleterious change to the channel structure. On the other hand, both the homozygous and the heterozygous individuals were phenotypically healthy and there were no clinical signs indicating the presence of the MH disposition.[27,28]

Our findings suggest that the Arg614Cys mutation is the cause of the MH phenotype in this family. The mutation was inherited over three generations and was only present in MHS individuals. Our results are supported by functional expression studies in which Arg614Cys mutant channels showed an increased sensitivity of intracellular calcium release to halothane and caffeine[13] or in which the calcium release was activated at lower depolarizing potentials.[29]

A second objective of this study was to assign MH susceptibility from identification of the familial mutation.[16] On the basis of the genotype/phenotype correlation described above we assigned the MHS diagnosis to eight further mutation carriers in this family without performing the invasive IVCT. These individuals, especially, profited from the identification of the familial RYR1 mutation and did not have to undergo the muscle biopsy; this was reflected in a much greater compliance on their part concerning the MH investigation. Individuals who do not carry the familial mutation should still undergo the IVCT because of the genetic complexity of MH.[16]

After establishing the MH disposition in the index patient, a commonly used testing strategy is to perform an IVCT on one parent in the first instance. If this produced a clear MHS diagnosis it would be possible to assume that the other parent is MHN and does not need to undergo the invasive IVCT because the likelihood of the other parent also being MH-susceptible is very small (1:10 000 to 1:60 000 where volatile anaesthetics are used[30,31]). With our family, this strategy could have had disastrous consequences for the second parent. Our results support the suggestion that both parents of a MHS subject should always be investigated.[32]

Our study has demonstrated that genetic data for MH status can in some cases provide additional diagnostic information and prove a valuable supplement to diagnostic testing for MH.

References

1 Kalow W. Inheritance of malignant hyperthermia: a review of published data. In: Britt BA, ed. *Malignant Hyperthermia.* Amsterdam: Martinus-Nijhoff, 1987; 155–79

2 Gronert GA. Malignant hyperthermia. In: Engel AG, Franzini-Armstrong C, eds. *Myology*, vol 2. New York: Mc Graw-Hill, 1994: 1661–78

3 Larach MG, Rosenberg H, Larach DR, Broennle M. Prediction of malignant hyperthermia susceptibility by clinical signs. *Anesthesiology* 1987; **66**: 547–50

4 Ellis FR, Halsall PJ, Christian AS. Clinical presentation of suspected malignant hyperthermia during anaesthesia in 402 probands. *Anaesthesia* 1990; **45**: 838–41

5 The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *Br J Anaesth* 1984; **56**: 1267–9

6 Ørding H, European Malignant Hyperthermia Group. In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH-Group: Results of testing patients surviving fulminant MH and unrelated low-risk subjects. *Acta Anaesthesiol Scand* 1997; **41**: 955–66

7 Allen GC, Larach MG, Kunselmann AR. The North American Malignant Hyperthermia Registry of MHAUS: Sensitivity and specificity of the caffeine-halothane contracture test. A report from the North American Malignant Hyperthermia Registry. *Anesthesiology* 1998; **88**: 579–88

8 Gillard EF, Otsu K, Fujii J, *et al.* A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia. *Genomics* 1991; **11**: 751–5

9 MacKenzie AE, Korneluk RG, Zorzato F. The human ryanodine receptor gene: its mapping to 19q13.1, placement in a chromosome 19 linkage group, and exclusion as the gene causing myotonic dystrophy. *Am J Hum Genet* 1990; **46**: 1082–9

10 McCarthy TV, Healy JMS, Heffron JJA, *et al.* Localisation of the malignant hyperthermia susceptibility locus to human chromosome 19q12–13.2. *Nature* 1990; **343**: 562–4

11 Ball SP, Johnson KJ. The genetics of malignant hyperthermia. *J Med Genet* 1993; **30**: 89–93

12 McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. *Hum Mutat* 2000; **15**: 410–7

13 Tong J, Oyamad H, Demaureux N, Grinstein S, McCarthy TV, MacLennan DH. Caffeine and halothane sensitivity of intracellular Ca2+ release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and or central core disease. *J Biol Chem* 1997; **272**: 26332–9

14 Larach MG, Mac Lennan DH. How carefully can we phenotype patients suspected of malignant hyperthermia susceptibility? *Anesthesiology* 1999; **90**: 645–8

15 McCarthy TV, O'Halloran J, The European Malignant Hyperthermia Group. Genotype phenotype correlation in malignant hyperthermia susceptibility. *Acta Anaesthesiol Scand* 1998; **42**: 206–9

16 Urwyler A, Deufel T, McCarthy T, West S for the European Malignant Hyperthermia Group. Guidelines for the molecular genetic detection of malignant hyperthermia susceptibility. *Br J Anaesth* 2001; in press

17 Phillips MS, Fujii J, Khanna VK, deLeon S, Yokobata K, De Jong PJ, MacLennan DH. The structural organisation of the human skeletal muscle ryanodine receptor (RYR1) gene. *Genomics* 1996; **34**: 24–41

18 Larach MG, Localio AR, Allen GC, *et al.* A clinical grading scale to

predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; **80**: 771–9

19 Lynch PJ, Krivosic-Horber, Reyford H, *et al.* Identification of heterozygous and homozygous individuals with the novel RYR1 mutation Cys35Arg in a large kindred. *Anesthesiology* 1997; **86**: 620–6

20 Deufel T, Sudbrak R, Feist Y, *et al.* Discordance, in a malignant hyperthermia pedigree, between in vitro contracture-test phenotypes and haplotypes for the MHS 1 region on chromosome 19q12–13.2, comprising the C1840-T transition in the RYR1 gene. *Am J Hum Genet* 1995; **56**: 1334–42

21 Serfas K, Bose D, Patel L, *et al.* Comparison of the segregation of the RYR1 C1840T mutation with segregation of the caffeine/halothane contracture test results for malignant hyperthermia susceptibility in a large Manitoba Mennonite family. *Anesthesiology* 1996; **84**: 322–9

22 Iles DE, Lehmann-Horn F, Scherer SW, *et al.* Localisation of the gene encoding the a2/d-subunit of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. *Hum Mol Genet* 1994; **3**: 969–75

23 Levitt RC, Olckers A, Meyers S, *et al.* Evidence for the localization of a malignant hyperthermia susceptibility locus to human chromosome 17q. *Genomics* 1992; **14**: 562–6

24 Robinson RL, Monnier N, Wolz W, *et al.* A genome wide search for susceptibility loci in three European malignant hyperthermia pedigrees. *Hum Mol Genet* 1997; **6**: 953–61

25 Sudbrak R, Procaccio V, Klausnitzer M, *et al.* Mapping of a further malignant hyperthermia susceptibility locus to chromosome 3q13.1. *Am J Hum Genet* 1995; **56**: 684–91

26 Ørding D, Islander G, Bendixen D, Ranklev-Twetman E. Between-center variability of results of the in vitro contracture test for malignant hyperthermia susceptibility. *Anesth Analg* 2000; **91**: 452–7

27 Quane KA, Keating KE, Healy JMS, *et al.* Mutation screening of the RYR1 gene in malignant hyperthermia: Detection of a novel Tyr to Ser mutation in a pedigree with associated central cores. *Genomics* 1994; **23**: 236–9

28 Pauli RM. Dominance and homozygosity in man. *Am J Med Genet* 1983; **16**: 455–9

29 Dietze B, Henke J, Eichinger HM, Lehmann-Horn F, Melzer W. Malignant hyperthermia mutation Arg615Cys in the porcine ryanodine receptor alters voltage dependence of Ca2+ release. *J Physiol (Lond)* 2000; **526**: 507–14

30 Ørding H. Incidence of malignant hyperthermia in Denmark. *Anesth Analg* 1985; **64**: 700–4

31 Caroll JB. Increased incidence of masseter spasm in children with strabismus anaesthetized with halothane and succinylcholine. *Anesthesiology* 1987; **67**: 559–61

32 Islander G, Bendixen D, Ranklev-Twetman E, Ørding H. Results of *in vitro* contracture testing of both parents of malignant hyperthermia susceptible probands. *Acta Anaesthesiol Scand* 1996; **40**: 579–84

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Isolated reduction of haematocrit does not compromise *in vitro* blood coagulation

B. M. Iselin[1], P. F. X. Willimann[1], B. Seifert[2], M. Casutt[1], T. Bombeli[3], M. P. Zalunardo[1], T. Pasch[1] and D. R. Spahn[1]*

[1]Institute of Anaesthesiology, University Hospital Zurich, Switzerland. [2]Department of Biostatistics, University of Zurich, Switzerland. [3]Division of Haematology, Department of Internal Medicine, University Hospital Zurich, Switzerland.

**Corresponding author: Institute of Anaesthesiology, University Hospital, Raemistrasse 100, CH-8091 Zürich, Switzerland*

Low haematocrit values are generally well tolerated in terms of oxygen transport but a low haematocrit might interfere with blood coagulation. We thus sampled 60 ml of blood in 30 healthy volunteers. The blood was centrifuged for 30 min at 2000 *g* and separated into plasma, which contained the platelet fraction, and packed red blood cells. The blood was subsequently reconstituted by combining the entire plasma fraction with a mixture of packed red blood cells, 0.9% saline, so that the final haematocrit was either 40, 30, 20, or 10%. Blood coagulation was assessed by computerized Thrombelastograph® analysis. Data were compared using repeated measures analysis of variance and post-hoc paired *t*-tests with Bonferroni correction. Decreasing the haematocrit from 40 to 10% resulted in a shortening of reaction time (*r*) and coagulation time (*k*), and an increase in angle α, maximum amplitude (MA) and clot strength (G) (all $P<0.02$). This pattern represents acceleration of blood coagulation with low haematocrit values. The isolated reduction in haematocrit, therefore, does not compromise *in vitro* blood coagulation.

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Avoiding allogeneic blood transfusions[1 2] and avoiding hypovolaemia[3 4] is important in the perioperative care of surgical patients. A treatment strategy tailored to both of these aims will result in periods of low haematocrit in patients undergoing surgical procedures associated with significant blood loss. In general, such acute haemodilution is well tolerated[5] but there are recent publications that raise concerns that a low haematocrit might compromise blood coagulation[6–8] and even recommend allogeneic blood transfusion to raise the haematocrit at least to 30% just to optimize blood coagulation.[6] It is indeed known that large volume infusions of colloids progressively compromise blood coagulation.[9–11] In contrast, moderate haemodilution with crystalloids may accelerate blood coagulation.[9 12 13] We thus studied the effect of a progressive reduction in haematocrit *per se* on blood coagulation.

Materials and methods

With approval of the Anaesthesia and Surgery Ethics Committee of the University Hospital Zurich and written informed consent, 30 healthy volunteers (24–51 yr of age) were enrolled into this study. Exclusion criteria were known cardiovascular, lung or liver diseases, history of bleeding diathesis, known alcohol, drug or nicotine abuse, treatment with heparin, or acetylsalicylic acid within 5 days before the study and treatment with non-steroidal anti-inflammatory drugs within 24 h of the study.

A total of 60 ml of blood was collected in six 10 ml graduated polypropylene tubes (Milian S.A., Geneva, Switzerland) containing 1 ml of buffered sodium citrate (0.129 M). Five aliquots were centrifuged for 30 min at 2000 *g*. The remaining aliquot served as the reference to determine the effect, if any, of blood handling, centrifugation and pipetting on blood coagulation. After centrifugation, the initial haematocrit was determined directly in the graduated tube. The blood was separated into packed red blood cells and platelet poor plasma with the entire buffy coat, i.e. plasma containing virtually all the platelets. In one of these aliquots, the blood was reconstituted without haematocrit manipulation. In the remaining four aliquots, a part of the packed red blood cells was replaced with 0.9%

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saline so that the final haematocrit, after mixing with the entire plasma and platelet fraction, yielded a final haematocrit of 40, 30, 20, or 10%, respectively. Platelets, haemoglobin, and haematocrit were subsequently measured in the reconstituted blood (Coulter® Ac T8, Coulter Corporation, Miami, FL, USA).

Blood coagulation was assessed using a computerized Thrombelastograph® Coagulation Analyser (CTEG® #3000, Haemoscope, Morton Grove, IL, USA) with celite activation.[14] The following variables of the TEG® trace were analysed: reaction time (*r*, normal value 12.0 (2.3) mm)—the time from the start of the recording until the amplitude reaches 2 mm; coagulation time (*k*, normal value 4.2 (1.6) mm)—the time from the end of reaction time (*r*) until the amplitude achieves 20 mm; maximum amplitude (MA, normal value 63.5 (4.5) mm) of the TEG® tracing represents the absolute strength of the clot; angle α (normal value 60.2 (6.7)°)—the angle formed by the slope of the TEG® tracing from the *r* to the *k* value. Clot lysis was represented by the percentage decrease in the area under the curve at 60 min (Lys60, normal value <15%) after MA.[9] One millilitre of citrated blood was pipetted into a tube containing 1% celite, and 340 ml of celite-activated citrated blood was added to a TEG® cup containing 20 ml 2 M $CaCl_2$ for recalcification. Clot strength (G) was calculated from the MA as: $G=(5000 \times MA)/(96-MA)$.[15 16]

Statistical analysis

The effect of blood centrifugation, pipetting and reconstitution was assessed by comparing TEG® variables before and after processing using paired *t*-tests. The effect of progressive *in vitro* haemodilution was assessed with repeated measures ANOVA and post-hoc paired *t*-test with Bonferroni correction. Data are presented as mean (SD). *P*-values less than 0.05 were considered significant.

Results

Blood handling including centrifugation did not affect blood coagulation (Table 1).

Progressive reduction of haematocrit from 40 to 10% did not result in compromised blood coagulation as assessed by TEG® (Fig. 1). The platelet count was unaffected, reaction time (*r*) and coagulation time (*k*) decreased, and angle α and MA increased with decreasing haematocrit levels. Clot strength (G) increased with decreasing haematocrit levels. Clot lysis at 60 min decreased minimally with the reduction in haematocrit.

Table 1 Effect of blood centrifugation, pipetting and reconstitution (centrifuged) on blood coagulation. Note, there are no significant differences. Hb=haemoglobin, HCT=haematocrit *r*=reaction time, *k*=coagulation time, MA=maximum amplitude, G=clot strength and Lys60=clot lysis at 60 min

	Non-centrifuged	Centrifuged	*P*
Hb (g dl^{-1})	14.0 (1.0)	13.9 (1.0)	0.697
HCT (%)	40.9 (2.9)	41.0 (2.9)	0.712
Platelets (10^9 $litre^{-1}$)	183 (44)	179 (46)	0.472
r (mm)	11.6 (4.5)	11.2 (4.2)	0.473
k (mm)	4.6 (2.0)	4.4 (1.6)	0.492
Angle α (°)	62.0 (9.9)	61.9 (9.0)	0.914
MA (mm)	59.5 (5.0)	59.3 (4.0)	0.757
G (10^3 dynes cm^{-2})	8.4 (1.9)	8.3 (1.7)	0.533
Lys60 (%)	4.4 (2.0)	4.2 (1.4)	0.445

Discussion

The current study indicates that an isolated reduction of haematocrit does not compromise *in vitro* blood coagulation. In contrast, with decreasing haematocrit, all TEG® variables unanimously changed towards an accelerated blood coagulation profile resulting in increased clot strength (G).

It was recently shown that there is virtually no thrombin generation in the absence of platelets.[17] With the addition of red blood cells, however, thrombin generation gradually recovered and it was speculated that red blood cells would participate in the haemostatic process through exposure of procoagulant phospholipids at their outer cell membrane.[17 18] In the presence of a normal number of platelets, as in the current study, *in vitro* blood coagulation appears not to be compromised significantly by a reduced number of red blood cells. Indeed, all TEG® variables indicated accelerated blood coagulation with a decreasing haematocrit resulting in an increased clot strength (G) (Fig. 1).

How relevant is this *in vitro* study for the clinical care of surgical patients? Of course, the *in vitro* situation is different from the clinical care of surgical patients, but only the *in vitro* situation allows the assessment of the isolated effect of a relevant change in haematocrit on blood coagulation. In surgical patients, low haematocrits are usually encountered after advanced surgical blood loss and asanguineous infusion therapy to maintain normovolaemia. Therefore, the patients have lost also coagulation factors and platelets. In this situation, coagulopathy will result from decreased levels of coagulation factors and platelets as well as the effects of dilution with crystalloids and colloids.[9] Interestingly, Mezzano and colleagues found that platelet dysfunction and severity of renal dysfunction but not the haematocrit were independent predictors for haemostatic disorders in uraemic patients.[19] Therefore, it may appear somewhat simplistic to advocate the use of allogeneic red blood cell transfusions for the specific purpose of optimizing blood coagulation.[6]

The use of TEG® analysis may also be criticized. We chose TEG® analysis because, in a variety of clinical situations, TEG® was the most sensitive method to predict surgical blood loss or the occurrence of bleeding complications.[20–25] TEG® is increasingly used in studies on blood coagulation[14 15 26] and *in vivo* and *in vitro* haemodilution results in similar TEG® changes in

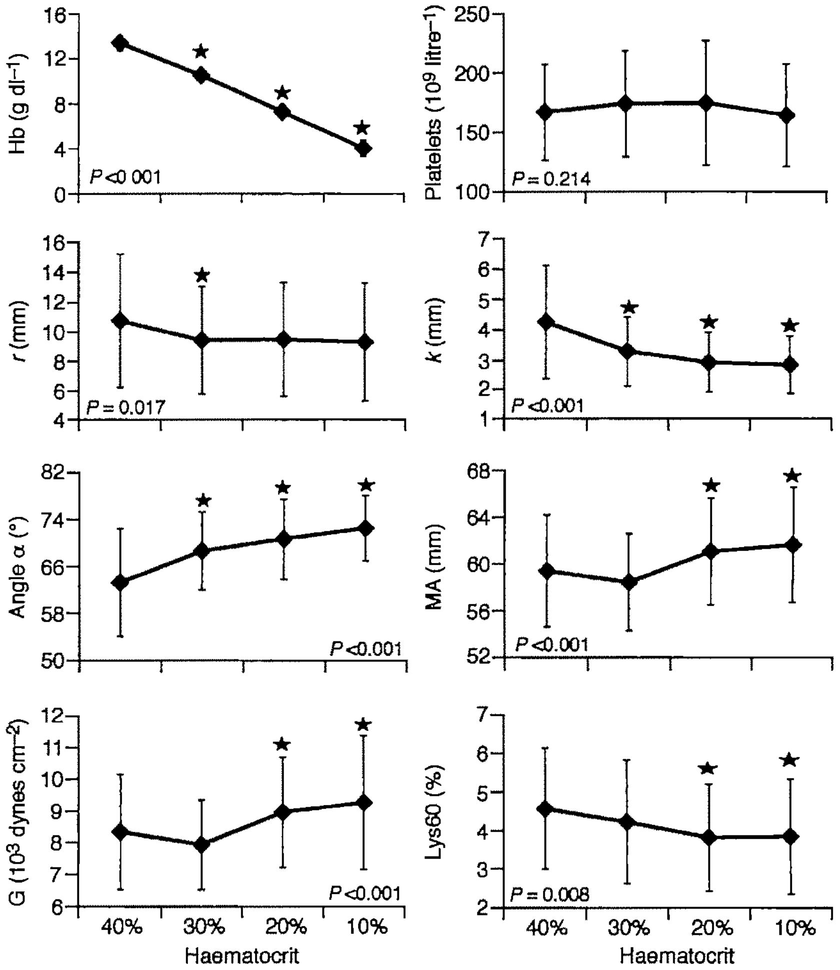

Fig 1 Effect of the isolated reduction in haematocrit from 40 to 10% on *in vitro* blood coagulation. *P* values refer to the overall ANOVA, * indicates $P<0.017$ *vs* haematocrit of 40%. Hb=haemoglobin, *r*=reaction time, *k*=coagulation time (*k*), MA=maximum amplitude, G=clot strength (G), and Lys60=clot lysis at 60 min

humans.[27] Interestingly, the results of the present study are in accordance with an *in vivo* study in rabbits demonstrating that a reduction of the haematocrit from 36 to 22% was not associated with an increased blood loss because of a subsequent standard splenic incision.[8] The current study suggests that a reduction of haematocrit even beyond this range is not associated with significantly compromised blood coagulation. The results are also in agreement with previous findings that clot strength (G) tended to be higher in platelet rich plasma when compared with whole blood.[16]

-The current study assessed the effect of an isolated decrease in haematocrit on *in vitro* blood coagulation with constant platelet count and unchanged coagulation factors. This is different from a previous study by Egli and colleagues.[9] where the effect of a progressive *in vitro* haemodilution with a concomitant dilution of platelets and coagulation factors was investigated. Accordingly, different results were found. At 60% haemodilution, corresponding to a haematocrit of approximately 17%, blood coagulation was largely unchanged and MA decreased.[9] In contrast, blood coagulation was accelerated in the current study at 20% haematocrit with an increase in MA (Fig. 1). This may be explained by preserved platelet count and coagulation factors.

In conclusion, the isolated reduction of the haematocrit appears not to compromise *in vitro* blood coagulation and recommendations to raise the haematocrit to at least 30% with the use of allogeneic blood transfusions to optimize blood coagulation[6] should be viewed with reservation considering the potential adverse effects of allogeneic blood transfusions.[1]

Acknowledgement

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References

1 Spahn DR, Casutt M. Eliminating blood transfusions: New aspects and perspectives. *Anesthesiology* 2000; **93**: 242–55
2 Hebert PC, Wells G, Blajchman MA, *et al.* A multicenter,

randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340**: 409–17

3 Younes RN, Rogatko A, Vydelingum NA, Brennan MF. Effects of hypovolemia and transfusion on tumor growth in MCA-tumor-bearing rats. *Surgery* 1991; **109**: 307–12

4 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; **315**: 909–12

5 Spahn DR, Leone BJ, Reves JG, Pasch T. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of nonoxygen-carrying and oxygen-carrying solutions. *Anesth Analg* 1994; **78**: 1000–21

6 Valeri CR, Crowley JP, Loscalzo J. The red cell transfusion trigger: has a sin of commission now become a sin of omission? *Transfusion* 1998; **38**: 602–10

7 Crowley JP, Metzger JB, Valeri CR. The volume of blood shed during the bleeding time correlates with the peripheral venous hematocrit. *Am J Clin Pathol* 1997; **108**: 579–84

8 Quaknine-Orlando B, Samama CM, Riou B, *et al*. Role of the hematocrit in a rabbit model of arterial thrombosis and bleeding. *Anesthesiology* 1999; **90**: 1454–61

9 Egli GA, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. An *in vitro* thrombelastography study. *Br J Anaesth* 1997; **78**: 684–9

10 Strauss RG, Stansfield C, Henriksen RA, Villhauer PJ. Pentastarch may cause fewer effects on coagulation than hetastarch. *Transfusion* 1988; **28**: 257–60

11 Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78**: 974–83

12 Ruttmann TG, James MFM, Aronson I. *In vivo* investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998; **80**: 612–6

13 Ruttmann TG, James MF, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–4

14 Camenzind V, Bombeli T, Seifert B, *et al*. Citrate storage affects Thrombelastograph® analysis. *Anesthesiology* 2000; **92**: 1242–9

15 Nielsen VG, Geary BT, Baird MS. Evaluation of the contribution of platelets to clot strength by thrombelastography in rabbits: the role of tissue factor and cytochalasin D. *Anesth Analg* 2000; **91**: 35–9

16 Khurana S, Mattson JC, Westley S, O'Neill WW, Timmis GC, Safian RD. Monitoring platelet glycoprotein IIb/IIIa-fibrin interaction with tissue factor-activated thromboelastography. *J Lab Clin Med* 1997; **130**: 401–11

17 Peyrou V, Lormeau JC, Herault JP, Gaich C, Pflliegger AM, Herbert JM. Contribution of erythrocytes to thrombin generation in whole blood. *Thromb Haemost* 1999; **81**: 400–6

18 Zwaal RF, Comfurius P, Bevers EM. Mechanism and function of changes in membrane-phospholipid asymmetry in platelets and erythrocytes. *Biochem Soc Trans* 1993; **21**: 248–53

19 Mezzano D, Tagle R, Panes O, *et al*. Hemostatic disorder of uremia: the platelet defect, main determinant of the prolonged bleeding time, is correlated with indices of activation of coagulation and fibrinolysis. *Thromb Haemost* 1996; **76**: 312–21

20 Chau TN, Chan YW, Patch D, Tokunaga S, Greenslade L, Burroughs AK. Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. *Gut* 1998; **43**: 267–71

21 Kang Y. Thromboelastography in liver transplantation. *Semin Thromb Hemost* 1995; **21** (Suppl 4): 34–44

22 Bayly PJ, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73**: 840–2

23 Steib A, Gengenwin N, Freys G, Boudjema K, Levy S, Otteni JC. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. *Br J Anaesth* 1994; **73**: 645–8

24 Williams GD, Bratton SL, Riley EC, Ramamoorthy C. Coagulation tests during cardiopulmonary bypass correlate with blood loss in children undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; **13**: 398–404

25 Ereth MH, Nuttall GA, Klindworth JT, *et al*. Does the platelet-activated clotting test (HemoSTATUS) predict blood loss and platelet dysfunction associated with cardiopulmonary bypass? *Anesth Analg* 1997; **85**: 259–64

26 Whitten CW, Greilich PE. Thrombelastography: past, present, and future. *Anesthesiology* 2000; **92**: 1223–5

27 Jamnicki M, Bombeli T, Seifert B, *et al*. Low- and medium-molecular-weight hydroxyethyl starch: Comparison of their effect on blood coagulation. *Anesthesiology* 2000; **93**: 1231–7

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A reduction in Type and Screen: preoperative prediction of RBC transfusions in surgery procedures with intermediate transfusion risks[†]

W. A. van Klei[1 2]*, K. G. M. Moons[1 2], A. T. Rheineck Leyssius[3], J. T. A. Knape[1], C. L. G. Rutten[4] and D. E. Grobbee[2]

[1]*Department of Peri-operative Care, Anesthesia and Pain Management,* [2]*Julius Centre for General Practice and Patient Oriented Research, University Medical Centre Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands.* [3]*Department of Anesthesiology and Intensive Care Medicine, Twenteborg Hospital, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands.* [4]*Department of Anesthesiology, Isala Clinics, Weezenlanden Hospital, PO Box 10500, 8000 GM Zwolle, The Netherlands*

**Corresponding author*

In many patients, a 'type and screen' procedure is routinely performed before surgery. However, most patients are not transfused after all. Can we predict, which surgical patients will and will not be transfused, to reduce the number of these investigations? We studied 1482 consecutive surgical patients with intermediate risk for transfusion. Multivariate logistic regression modelling and the area under the Receiver Operating Characteristic curve (ROC area) were used to quantify how well age, gender, surgical procedure, emergency or elective surgery and anaesthetic technique predicted transfusion, and whether the preoperative haemoglobin concentration had added predictive value. Gender, age ≥70 yr, and type of surgery were independent predictors of transfusion, with a ROC area of 0.75 (95% CI: 0.72–0.79). Validating this model with an easily used prediction rule in a second patient population yielded a ROC area of 0.70 (95% CI: 0.63–0.77). With this rule type and screen could correctly be withheld in 35% of these patients. In the remaining 65% of the patients, a further reduction in type and screen investigations of 15% could be achieved using the preoperative haemoglobin concentration. Using a simple prediction rule, preoperative type and screen investigations in patients who have to undergo surgery procedures with intermediate transfusion risk can be avoided in about 50%. This may reduce patient burden and hospital costs (on average: 3 million US$ per 100 000 procedures).

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Transfusion of blood (red blood cells or RBC) is sometimes necessary in patients having surgery. A 'type and screen' is done preoperatively to prevent complications from incompatibility between donor and recipient or the existence of irregular antibodies. This procedure is much cheaper than full cross matching, and gives the same immunohaematological safety.[1–4] Generally, physicians type and screen patients who might need a perioperative transfusion (commonly based on past experience with the surgical procedure as single predictor). However, most patients who are typed and screened before surgery will not require a transfusion, which means unnecessary patient burden and costs. It would be efficient to further classify patients according to their risk of transfusion using objective and easy obtainable information. Various prediction rules have been developed (especially in orthopaedic surgery), but a laboratory value (preoperative haemoglobin concentration or haematocrit) was always included.[5] However, it would be even more efficient if the same predictive accuracy could be obtained without the need for laboratory tests.[6–9]

We developed and validated a rule based on patient and surgery characteristics, to predict blood transfusion in

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patients undergoing surgery with intermediate transfusion risk (1–30%). Subsequently, we evaluated how knowing the preoperative haemoglobin concentration could increase the predictive accuracy of this prediction rule.

Methods

Patients

We studied 1482 patients (aged 18–98 yr) with intermediate transfusion risk ('type and screen patients'), undergoing surgery in the Twenteborg Hospital in The Netherlands, in 1998. This hospital is a 638-bed non-university hospital in which neurosurgery and cardiac surgery are not performed. The classification of type and screen patients was based on the current transfusion guide. This divides patients into three surgical groups according to expert opinion. Group A patients have low expected risk for transfusion (0–1%; e.g. arthroscopy or ear surgery), group B patients have intermediate risk for transfusion (1% to approximately 30%; e.g. cholescystectomy or hysterectomy) and group C are high risk patients (more than 30%; e.g. aortic surgery). In group A patients, type and screen is never done (78% of all patients). Patients belonging to group B are always typed and screened, but blood is not stored (16%). Group C patients are always typed and screened and blood is stored (6%). Of all patients in group A, nearly 2% received transfusions. In group B and C the incidence of transfusion was 19% and 43%, respectively. This study evaluates only group B patients ('type and screen patients'). None of the 1482 patients donated autologous blood preoperatively.

Outcome

The outcome was defined as any allogeneic RBC transfusion (defined as transfusion of one or more units packed cells) on the day of surgery or the first postoperative day. The transfusion decision was made by individual clinicians (anaesthesiologists and surgeons). A rigid protocol was not in use, but in general blood was given when the haemoglobin level was below 10 g dl^{-1} (6.0 mmol $litre^{-1}$).

Potential predictor variables

Age, gender, surgery procedures, whether it was an emergency operation (yes/no), the anaesthetic technique and the preoperative haemoglobin level were evaluated as potential predictors. As 39 different surgical procedures were used, they were allocated into 5 categories based on actual risk (occurrence) of transfusion: Group 1 contained only laparoscopic cholecystectomy (transfusion incidence <5%); Group 2 mastectomy and transurethral resection of tumour (TURT) or prostate (TURP) (transfusion incidence 5–9%); Group 3 open cholescystectomy, vaginal hysterectomy, Caesarean section, surgery for urine incontinence or vaginal prolapse (10–19%); Group 4 non-cardiac thoracic surgery (e.g. lobectomy), vascular (arterial) surgery (e.g. femoro-popliteal bypass), prostate enucleation and endometrial cancer surgery (20–29%); Group 5 abdominal and vaginal hysterectomy, hip fracture surgery, revision knee prosthesis, leg amputation, gastro-enterostomy, colon-resection and radical abdominal hysterectomy (30% or more). Anaesthetic technique was defined as a dichotomous variable: a single form of anaesthesia (general, regional or local) compared with a combination anaesthesia (general anaesthesia combined with epidural analgesia). Although in principle a potential predictor, we decided not to include the identity of the surgeon and anaesthesiologist in the model, as they are hard to extrapolate to other hospitals and the aim was to derive an easy and widely applicable prediction rule.

Data collection

The hospital ethics committee approved the study. All data were collected retrospectively from the hospital information system. There were no missing data on any of the predictor or outcome variables, except for the haemoglobin concentration. In 152 patients (10%) it was not measured preoperatively.

Analysis

In the present study, two data sets were randomly selected from all 1482 patients: a derivation set of approximately 75% (1151 patients) and a validation set of approximately 25% (331 patients). SPSS release 9.0 for Windows was used in the analysis (Windows NT 4.0, DELL computer). In the derivation set the association between each predictor and transfusion outcome was quantified using univariable logistic regression modelling. This type of analysis is an alternative to using chi-square tests and gives similar results. In the analysis, surgery was included as four indicator variables (groups 2 to 5) with group 1 as the reference. As the incidence of transfusion in patients aged 18 to 69 was between 10% and 20% in each decade, whereas in patients aged over 70 the incidence increased more rapidly, age was included in the model after dichotomization at 70. After univariate analyses, multivariable logistic regression modelling was applied in order to obtain a prediction model including the independent predictors of transfusion outcome only. This was done by a two-step approach. As age, gender, type of surgery (again included as four indicators), elective surgery and anaesthetic procedure are much easier to obtain, we first evaluated whether these had independent value in the prediction of perioperative transfusion. In this, the interaction between type of surgery and anaesthetic technique was evaluated as well, since both are closely related (regional anaesthesia may reduce blood loss). Subsequently, the added predictive value of the preoperative haemoglobin concentration was evaluated. The full model was reduced by manually (i.e. not automatically) deleting non-significant variables. Predictors with odds ratios that differed significantly from one, defined as odds ratio with *P*-value <0.10 using log likelihood ratio testing, were considered as independent predictors and retained in the final model. This is commonly done in prognostic research.[10]

To obtain an easily applicable prediction or scoring rule, the regression coefficients (=ln(OR)) of the predictors in the final model were divided by the smallest coefficient and rounded to the nearest integer. For each subject a score was estimated by assigning points for each variable present and adding the results. The reliability of our prediction rule (goodness of fit) was quantified by using the Hosmer and Lemeshow test. This test is used to compare observed probabilities with predicted probabilities. A high *P*-value of this test (>0.20) indicates that there is no difference between both probabilities, which means good fit of a model.[11] The ability of the model to discriminate between patients with and without transfusion was quantified by using the area under the Receiver Operating Characteristic curve (ROC area).[10–12] The ROC area can range from 0.5 (no more predictive than a coin flip) to 1.0 (perfect discrimination). A value over 0.7 can be interpreted as reasonable or fair, and over 0.8 as good.[13] Differences in ROC area were used to quantify the difference in discriminative ability between full and reduced models taking into account the correlation between the models as they were based on the same cases.[14]

Table 1 Patient characteristics of derivation and validation set. Values are numbers and percentages between parentheses. # Values are mean and standard deviation between parentheses. * Procedures are listed in the text

	Derivation set *n*=1151	**Validation set** *n*=331
Mean age (years)		
transfused patients	62 (21.3)#	62 (20.3)
non-transfused patients	56 (18.3)	58 (18.8)
Age (%)		
18–69 yr	790 (69)	218 (66)
≥70 yr	361 (31)	113 (34)
Gender (%)		
male	404 (35)	119 (36)
female	747 (65)	212 (64)
Anaesthetic technique (%)		
single type anaesthesia	1052 (91)	307 (93)
combined anaesthesia	99 (9)	24 (7)
Surgery procedures*(%)		
group 1	121 (11)	23 (7)
group 2	295 (26)	94 (28)
group 3	356 (31)	93 (28)
group 4	94 (8)	24 (7)
group 5	285 (25)	97 (29)
Type of surgery (%)		
elective	787 (68)	226 (68)
emergency	364 (32)	105 (32)
Transfusion (%)	208 (18)	69 (21)

The performance of the rule was tested in the validation set and the resulting ROC area was compared with the derivation set. A ROC area reflects the overall added value of a model and does not directly indicate its clinical value.[15 16] Therefore, in the validation set, we estimated the absolute number of correctly predicted transfused and not transfused patients for the various risk scores of the rule.

Results

Table 1 shows the comparison of patient characteristics of the derivation and validation set. There were no major differences between the two sets. The transfusion rates for the derivation and validation set were 18.1% (*n*=208) and 20.8% (*n*=69), respectively.

In the univariate analysis (Table 2) all variables were significantly associated with transfusion. The odds ratios of the four indicators for surgery (groups 2 to 5) indicate the relative risk of transfusion for that group, compared to the reference group 1 (e.g. procedures within group 3 have a 4.1 times higher risk of transfusion than those of group 1). After

Table 2 Association of each variable with the incidence of transfusion. # Reference category. * Surgery procedures were included as four indicator variables with group 1 as the reference category. ¶ mean. † OR per g dl^{-1} increase in haemoglobin concentration. OR=odds ratio;. 95% CI=95% confidence interval; LLR=log likelihood ratio test

Determinant	**Transfused**	**Not transfused**	**OR (95% CI)**	***P*-value (LLR)**
Age (%)				
18–69 years	110 (14)	680 (86)	#	
≥70 years	98 (27)	263 (73)	2.3 (1.7–3.1)	<0.001
Gender (%)				
male	49 (12)	355 (88)	#	
female	159 (21)	588 (79)	2.0 (1.4–2.8)	<0.001
Anaesthetic technique (%)				
single type anaesthesia	167 (16)	885 (84)	#	
combined anaesthesia	39 (39)	60 (61)	3.4 (2.2–5.3)	<0.001
Surgery procedures* (%)				
group 1	5 (4)	116 (96)	#	
group 2	18 (6)	277 (94)	1.5 (0.5–4.2)	0.425
group 3	53 (15)	303 (85)	4.1 (1.6–10.4)	0.002
group 4	25 (27)	69 (73)	8.4 (3.1–23.0)	<0.001
group 5	107 (38)	178 (62)	13.9 (5.5–35.2)	<0.001
Type of surgery (%)				
elective	112 (14)	675 (86)	#	
emergency	96 (26)	268 (74)	2.2 (1.6–2.9)	<0.001
Preoperative haemoglobin (g dl^{-1})	13.4¶	11.5¶	0.4 (0.3–0.5)†	<0.001

Table 3 Association of each variable with the incidence of transfusion in the multivariate logistic model. * Procedures per group are listed in the text; group 1 is the reference group. # The score of each predictor was obtained by dividing the corresponding regression coefficient by the smallest coefficient (0.524) and rounded to the nearest integer. 95% CI=95% confidence interval; OR=odds ratio

Determinant	Regression coefficient (95% CI)	OR (95% CI)	*P*-value	Score#
Gender (woman)	0.629 (0.20; 1.06)	1.9 (1.2;2.9)	0.004	1
Age ≥70	0.546 (0.18; 0.90)	1.7 (1.2;2.5)	0.003	1
Surgery procedure*				
group 2	0.524 (−0.52; 1.06)	1.7 (0.6;4.8)	0.324	1
group 3	1.291 (0.35; 2.23)	3.6 (1.4;9.3)	0.007	2
group 4	2.287 (1.26; 3.32)	9.8 (3.5;27.8)	< 0.001	4
group 5	2.386 (1.45; 3.33)	10.9 (4.2;27.9)	< 0.001	5
Intercept (constant)	−3.701 (−4.67;−2.73)		< 0.001	

entering age, gender, surgery procedure and emergency surgery into a multivariate logistic model, all were independently associated with transfusion (Table 3), except emergency surgery (OR 1.26; 95% CI: 0.84–1.88). The ROC area of this first model was 0.75 (95% CI: 0.71–0.79). As further exclusion of variables from this model significantly reduced the ROC area, the model with dichotomized age, gender and surgery procedure was defined as the final prediction model. Addition of anaesthetic technique (including the interaction terms with surgery procedure) to this model showed no added value in the prediction of transfusion: the ROC area remained 0.75. (For the estimation of the added value of the preoperative haemoglobin concentration see below.) Its ROC area in the validation set was 0.71 (95% CI: 0.64–0.78). The model's estimated risks of transfusion were comparable to the observed risks, which indicated a good model fit (the *P*-value of the Hosmer and Lemeshow test was 0.98).

This final model was transformed into an easily used scoring rule by dividing each regression coefficient by the smallest coefficient (0.524) and rounded to the nearest integer (last column of Table 3): *1*gender + 1*age ≥70 + (1, 2, 4 or 5)*surgery procedure.* Being a woman counts for 1 point, age ≥70 for 1 point, and surgery procedure for 1, 2, 4 or 5 points (for groups 2, 3, 4 and 5, respectively). Such a scoring rule can be considered as one overall predictor test, including several predictor variables. The score can be considered as its (test) result and can be estimated for each patient by assigning the points for each predictor present and adding these points. For instance, a 72-year-old man who will undergo a colon-resection, receives a score of 6 (0 + 1 + 5). In both datasets the score ranged from 0 to 7. The ROC area of the transformed prediction rule was 0.75 (95% CI: 0.71–0.78) and 0.70 (95% CI: 0.63–0.77) in the derivation and validation set, respectively (Fig. 1).

This prediction rule can be used preoperatively to distinguish patients who will and will not be transfused and therefore should and should not be typed and screened. Table 4 shows the actual number of transfused and not transfused patients across score categories (and across corresponding risk of transfusion as estimated by the untransformed model, i.e. second column of Table 3), after the rule was applied to the validation set.

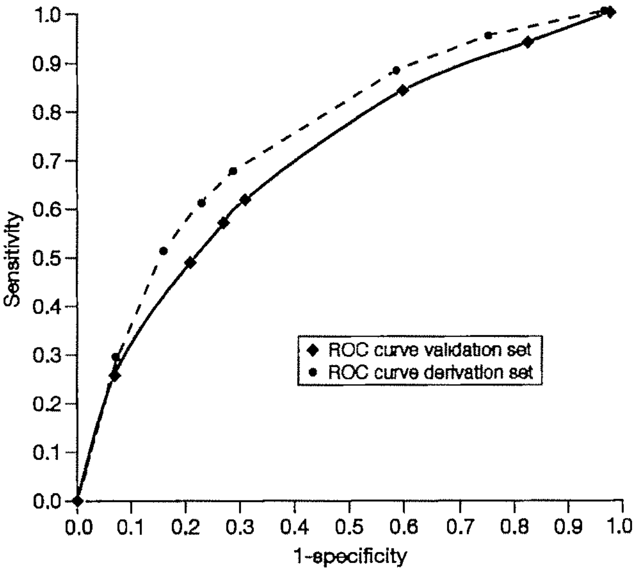

Fig 1 ROC curve of the transformed prediction rule (Table 3). Each bullet indicates a score threshold from 0 (upper-right) to 7 (bottom-left). For example, a score threshold of >2 gives a sensitivity of 0.84 and a specificity of 0.40 (1–0.60).

From Table 4 one can directly obtain the predictive value for transfusion per score category (reading the table vertically). For example, of all 115 patients with score ≤2 (or risk of transfusion ≤10%), 104 patients were indeed not transfused, yielding a negative predictive value of 90%. In the group of patients with score ≥5, 39 of the 111 were indeed transfused; a positive predictive value of 35%. Table 4 also enables to estimate the sensitivity and specificity at different score thresholds (reading the table horizontally). For example, introducing a threshold at 2, a score ≤2 will be considered as test negative and a score >2 will be considered as test positive. This means that, according to the rule, a test negative patient will not be transfused and does not need to be typed and screened, whether a test positive patient will be transfused and needs to be typed and screened. Using this

Table 4 Distribution of transfused and not transfused patients in the validation set, according to the score of the rule (and to the corresponding risk of transfusion). Values are presented as absolute numbers and as percentages of the 'Total' column between parentheses. # Categories of the score estimated from the (transformed) scoring rule (Table 3). *Risk or probability of transfusion estimated by the untransformed prediction model (Table 3) that correspond to the score from the first row: Risk=1/(1 + exp −(−3.701 + 0.629*gender +0.546*age ≥70 + 0.524*group2 + 1.291*group3 + 2.287*group4 + 2.386*group5)). *n*=number of subjects per score (risk) category.

Score by the rule# **Risk of transfusion* (%)**	**≤2** **≤10**	**3 and 4** **11–20**	**≥5** **≥21**	**Total**
Transfused	11 (16)	19 (26)	39 (58)	69 (100)
Not transfused	104 (40)	86 (32)	72 (28)	262 (100)
n	115 (35)	105 (31)	111 (34)	331 (100)

threshold of ≤2 (or transfusion risk ≤10%), the specificity was 40% (104/262) with 60% unnecessary type and screen procedures, whereas the sensitivity was 84% (19+39/69) with 11 (16%) missed transfused patients.

This 16% of patients who needed transfusion and who would not have been tested, was only 2% less than using a model with type of surgery as a single predictor. Because age and gender are easily obtainable, we decided to leave them in the model. The sensitivity and specificity of all possible score thresholds can be obtained from the ROC curve in Figure 1.

We wished to reduce the number of unnecessary type and screen procedures (i.e. to obtain a high specificity). We tested whether the preoperative haemoglobin concentration (preopHb), when added to the former prediction model (Table 3), contributed useful information. Adding preopHb to the previous model of Table 3, the ROC area increased from 0.71 to 0.80 (95% CI: 0.74–0.86) in the validation set. In absolute numbers the percentage of missed transfused patients decreased from 16% to 12%. We reasoned that it would therefore be inefficient to include preopHb in the initial prediction model, as it led to only a small decrease (4%) in missed transfusions at the expense of a haemoglobin measurement in all patients. Nevertheless, using the preopHb additionally *after* the application of the rule, i.e. only measuring the preoperative haemoglobin level among those patients with score >2, a further reduction in the number of unnecessary type and screen procedures *was* achievable. Of the 216 patients with score >2 (Table 4), 31 were excluded due to missing values on preopHb, leaving 185. Although we evaluated preopHb as a continuous as well as a dichotomous predictor variable, we decided to use the dichotomised form (at 14 g dl^{-1}) to enhance applicability, as there was no difference in predictive accuracy. Table 5 shows the results and can be read in the same way as Table 4. By withholding type and screen procedures in all patients with a preopHb level ≥14.0 g dl^{-1}, a *further* reduction in type and screen investigations of 24% could be achieved at the expense of another five missed transfused patients. Other haemoglobin thresholds yielded worse results.

Table 5 Distribution of transfused and not transfused patients according to the preoperative haemoglobin concentration in the patients from Table 4 with score >2. Values are presented as absolute numbers and as percentages of the 'Total' column between parentheses. * Preoperative haemoglobin concentration in g dl^{-1}. *n*=number of subjects per haemoglobin category

Hb (g dl^{-1})*	**<14.0**	**≥14.0**	**Total**
Transfusion +	44 (90)	5 (10)	49 (100)
Transfusion −	97 (71)	39 (29)	136 (100)
n	141 (76)	44 (24)	185 (100)

Figure 2 summarizes the results. Using the scoring rule with a threshold of ≤2 and subsequently the preopHb level at a threshold of ≥14.0 g dl^{-1}, type and screen would be withheld in about 50% of all patients undergoing surgery procedures with intermediate transfusion risk (35% plus 24% of 65%), with 16 (23%) missed transfusions. We investigated the characteristics of the missed transfused patients in the total population of 1482 patients (derivation and validation set together). The prediction rule and subsequent use of the preoperative haemoglobin concentration would miss 55 (20%) transfused patients (Table 6). On average, they required 2.5 units RBC per subject (95% CI: 2.1–2.9) and 82% of them (45 subjects) required no more than 2 units. Two patients required 8 and 10 units. They were emergency patients who were re-operated due to postoperative haemorrhage.

Discussion

To reduce the number of unnecessary preoperative type and screen procedures, we defined an easily applicable scoring rule containing three simple variables (gender, age, and surgery procedure) to predict transfusion in patients undergoing surgical procedures with intermediate transfusion risk.

Some comments are necessary. First, the prediction rules were based on data from one particular hospital. It is known that there are large differences in blood use between hospitals.[17–23] Although we have tried to show the robustness of the rule by testing it in a second dataset of our hospital, further research has to be done to validate the rule in other hospitals.

Second, the transfusion trigger was a haemoglobin level of 10 g dl^{-1} as was recommended formerly.[24–26] Currently, fewer patients are transfused as RBC transfusion is now based on the patient's risk for developing inadequate tissue oxygenation, which decreases the transfusion trigger to a haemoglobin level between 6 and 10 g dl^{-1}.[27–35] This means that when the proposed prediction rule (including the subsequent preoperative haemoglobin measurement) is applied in current practice, the yearly number of (missed) transfusions will be lower. Rehm *et al.*, for example, found a 26% decline in the number of RBC transfusions when the modern recommendations for transfusions were used.[4] This can be inferred from Table 6: the large majority of patients

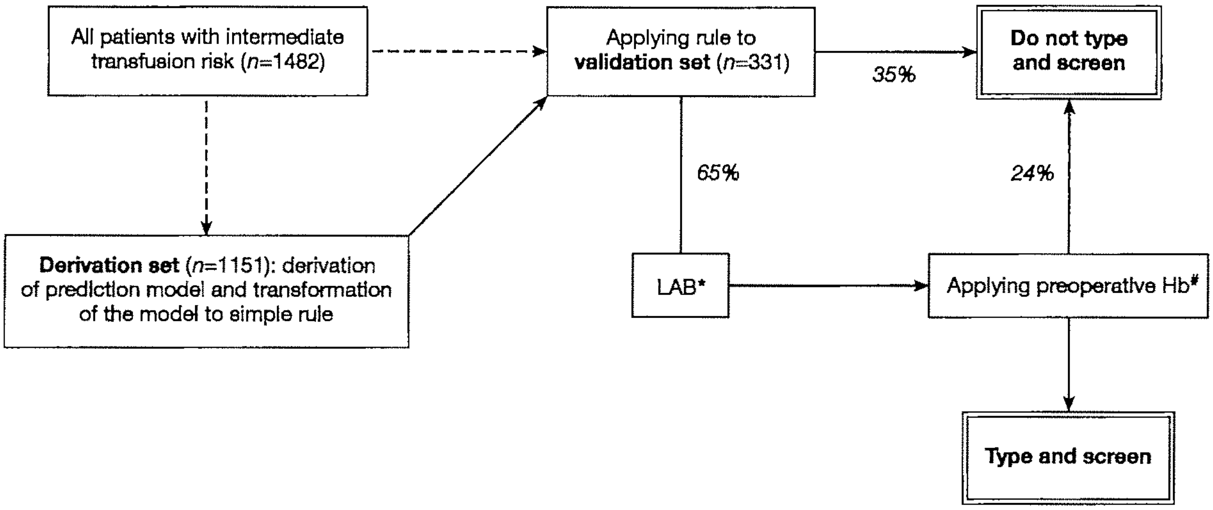
All patients with intermediate transfusion risk (n=1482)
Applying rule to validation set (n=331)
35%
Do not type and screen
65%
24%
Derivation set (n=1151): derivation of prediction model and transformation of the model to simple rule
LAB*
Applying preoperative Hb#
Type and screen

Fig 2 Flow chart of the results of this study after using the scoring rule at a threshold of score >2 and a preoperative haemoglobin concentration of 14.0 g dl^{-1}. [#]Preoperative haemoglobin concentration. *LAB: patients have to go to the laboratory, and two blood samples have to be taken; one to measure the preoperative Hb and one to investigate eventually the blood group.

received only 2 units packed cells or less, and would likely not now be transfused. However, although the number of wrongly predicted transfusions will likely be lower, the question about the acceptability of the remaining missed transfusions still exists. As can be seen in Table 6, an emergency transfusion seemed in general not probable (except for two patients who needed re-operation). If a patient is not typed and screened and massive haemorrhage occurs, colloids must be administered and the patient typed and screened. If, however, the patients' blood group is not available on time, 0$^-$ blood can always be administered even though the presence or absence of irregular erythrocyte antibodies is not yet known.[36] Furthermore, the risk of adverse reactions would be low anyway, given the low prevalence of these antibodies in the general population (2.5%).[37–40] We estimated that in only 0.1% of all transfusions for procedures with intermediate transfusion risk irregular antibodies would be a problem. (The 10 patients in Table 6 who required more than 2 units packed cells count for 3.6% of all transfusions; 2.5%*3.6% = 0.1%.)

Table 6 Surgery and transfusion characteristics of missed transfused patients (n=55) after application of the scoring rule and the preoperative haemoglobin concentration (derivation and validation set combined). [¶]Between parentheses the individual number of units RBC of the patients who required >2 units. [#]TUR=transurethral resection of prostate or tumour. *PreopHb= preoperative haemoglobin concentration

Surgery procedure	Patients (n)	Patients (n) with >2 units transfused (no. of units RBC)[¶]
After application of the scoring rule:		
TUR prostate/tumour[#]	17	5 (3; 3; 4; 4; 6)
cholecystectomy (laparoscopically/open)	10	2 (8; 10)
mastectomy with lymph node dissection	8	0
After additional application of preopHb*:		
abdominal hysterectomy	6	0
hip fracture surgery	4	0
lobectomy (lung)	3	1 (5)
peripheral artery surgery	3	1 (4)
colon resection	1	0
prostate adenoma enucleation	2	1 (5)
revision knee prosthesis	1	0

Finally, ASA-classification and body mass index are predictors of transfusion.[5–7 9 41] Unfortunately, these variables were not available for most of our patients. This limits the results of the study, although body mass index alone is an objective parameter, but the ASA-classification is proven to be subjective.[42 43]

The results of this study support previous work. All predictors for transfusion in surgery found in this study (gender, age over 70, surgery procedure and preoperative haemoglobin concentration) were also found by others.[5–9 20 41 44–46] However, direct comparison of our rule with other prediction models is difficult as most studies evaluated a particular type of surgery. One study of different types of surgery showed that complexity of surgery procedure, age and preoperative haemoglobin concentration significantly determined the need for perioperative RBC transfusion.[6] Most studies included at least one laboratory value in their initial prediction model (preoperative haemoglobin concentration or haematocrit).[5–9 41] Only one study described a rule without a laboratory value, which included similar predictors (e.g. gender) as we found.[47] This study only assessed total hip replacement and the outcome was blood loss rather than transfusion. We are the first to construct a prediction rule for surgical transfusion in procedures with intermediate transfusion risk without a laboratory value.

We suggest using our prediction rule at a threshold score of <2 or an estimated risk <10%, as was done by Weber in his model for preoperative prediction of transfusion in cancer surgery.[48] Sensitivity and specificity corresponding to this threshold (84% and 40%, respectively) are obtained in a prognostic setting and should not be confused with (usually much higher) estimates obtained in a diagnostic setting. Subsequently, we used the preoperative haemoglobin level at a threshold of $\geqslant 14.0$ g dl^{-1}. These threshold choices are arbitrary. One could use other thresholds in the scoring rule of Table 4 and the haemoglobin level, though leading to other percentages of misclassifications (Fig. 1).

We assumed that the average direct costs of type and screen are about US$ 80.[48–50] Using the prediction rule, 35% of all type and screen investigations in intermediate risk surgery procedures could be avoided, giving a reduction in costs of 3 million dollars per 100 000 of these procedures (35 000*$80). When the preoperative haemoglobin concentration is used additionally, a further reduction in costs seems achievable, although the measurement costs of the haemoglobin concentration have to be taken into account. Further cost-effectiveness analyses, including the 'costs' of the missed transfusions, should be done and is topic for further research.

In conclusion, we believe that prediction of blood transfusion in patients having surgery with intermediate transfusion risks is feasible using the rule we have developed together with the preoperative haemoglobin concentration. Using these predictors, the number of preoperative type and screen investigations will be reduced by about 50% leading to a considerable reduction in costs.

References

1 Atrah HI, Galea G, Urbaniak SJ. The sustained impact of a group and screen and maximum surgical blood ordering schedule policy on the transfusion practice in gynaecology and obstetrics. *Clin Lab Haem* 1995; **17**: 177–81

2 Riedler GF. "Type and screen": die Immunhamatologische Sicherheit ist gewahrleistet und die Kosten werden gesenkt. [English summary] *Schweiz Med Wochenschr* 1996; **126**: 1946–51

3 Ng SP. Blood transfusion requirements for abdominal hysterectomy: 3-year experience in a district hospital (1993–1995). *Aust N Z J Obstet Gynaecol* 1997; **37**: 452–7

4 Rehm JP, Otto PS, West WW, *et al.* Hospital-wide educational program decreases red blood cell transfusions. *J Surg Res* 1998; **75**: 183–6

5 Nuttall GA, Santrach PJ, Oliver-WC J, *et al.* The predictors of red cell transfusions in total hip arthroplasties. *Transfusion* 1996; **36**: 144–9

6 Ong AH, Sim KM, Boey SK. Preoperative prediction of intra and postoperative red blood cell transfusion in surgical patients. *Ann Acad Med Singapore* 1997; **26**: 430–4

7 Keating EM, Meding JB, Faris PM, Ritter MA. Predictors of transfusion risk in elective knee surgery. *Clin Orthop* 1998; 50–9

8 Larocque BJ, Gilbert K, Brien WF. Prospective validation of a point score system for predicting blood transfusion following hip or knee replacement. *Transfusion* 1998; **38**: 932–7

9 Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1999; **81**: 2–10

10 Harrel FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**: 361–87

11 Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: J.Wiley and sons, 1989; 140–5

12 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic curve. *Radiology* 1982; **143**: 29–36

13 Weinstein MC, Fineberg HV. *Clinical Decision Analysis*. Philadelphia: WB Saunders, 1980

14 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; **148**: 839–43

15 Moons KGM, Stijnen T, Michel BC, *et al.* Application of treatment thresholds to Diagnostic-test Evaluation: An alternative to the comparison of areas under the Receiver Operating Characteristic Curves. *Med Decis Making* 1997; **17**: 447–54

16 Moons KGM, van Es G, Michel BC, Buller HR, Habbema JDF, Grobbee DE. Redundancy of Single Diagnostic Test Evaluation. *Epidemiology* 1999; **10**: 276–81

17 Carson JL, Spence RK, Poses RM, Bonavita G. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988; **340**: 727–9

18 The Sanguis study group. Use of blood products for elective surgery in 43 European hospitals. *Trans Med* 1994; **4**: 251–68

19 Carson JL, Duff A., Poses RM, et *al.* Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1055–60

20 Baele P, Beguin C, Waterloos H, *et al.* The Belgium BIOMED Study about transfusion for surgery. *Acta Anaesthesiol Belg* 1998; **49**: 243–303

21 Capraro L. Transfusion practices in primary total joint replacements in Finland. *Vox Sang* 1998; **75**: 1–6

22 Surgenor DM, Churchill WH, Wallace EL, *et al.* The specific hospital significantly affects red cell and component transfusion practice in coronary artery bypass graft surgery: a study of five hospitals. *Transfusion* 1998; **38**: 122–33

23 Carson JL, Duff A, Berlin JA, *et al.* Perioperative blood transfusion and postoperative mortality. *JAMA* 1998; **279**: 199–205

24 Adams RC, Lundy JS. Anesthesia in cases of poor surgical risk. Some suggestions for decreasing the risk. *Surg Gynecol Obstet* 1942; **74**: 1011–19

25 Kowalyshyn TJ, Prager D, Young J. A review of the present status of preoperative hemoglobin requirements. *Anesth Analg* 1972; **51**: 75

26 Finch CA, Lenfant C. Oxygen transport in man. *N Engl J Med* 1972; **286**: 407–15

27 National Institute of Health (Bernstein M). Perioperative red blood cell transfusion. *JAMA* 1988; **250**: 2700–3

28 Stehling L, Simon TL. The red blood cell transfusion trigger. *Arch Pathol Lab Med* 1994; **118**: 429–34

29 Task force on blood component therapy. Practice guidelines for blood component therapy. A report by the American Society of Anesthesiologists task force on blood component therapy. *Anesthesiology* 1996; **84**: 732–47

30 Spence RK. Emerging trends in surgical blood transfusion. *Semin Hematol* 1997; **34**: 48–53

31 Loo S, Low TC. Perioperative transfusion strategies: a national

survey among anaesthetists. *Ann Acad Med Singapore* 1997; **26**: 193–9

32 Spence RK. Anemia in the patient undergoing surgery and the transfusion decision. A review. *Clin Orthop* 1998; 19–29

33 Weiskopf RB. Do we know when to transfuse red cells to treat acute anemia? *Transfusion* 1998; **38**: 517–21

34 Carson JL, Terrin ML, Barton FB, et *al.* A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion* 1998; **38**: 522–9

35 McFarland JG. Perioperative blood transfusions: indications and options. *Chest* 1999; **115**: 113S–121S

36 Flebig E. Safety of blood supply. *Clin Orthop Res* 1998; **357**: 6–18

37 Wittkopf D, Grundmann A, Sibrowski W, von Eisenhart RB, Kuhnl P. Analyse irregularer Antikorper in der Abteilung fur *Transfusions*medizin am Universitats-Krankenhaus Hamburg-Eppendorf von 1984–1988. [English summary] *Infusionstherapie* 1990; **17**: 280–2

38 Burin-des RN, Nasr O. Recherche des anticorps irreguliers erythrocytaires par la methode du gel-test. Analyse de 35,882 echantillons. [English summary] *Rev Fr Transfus Hemobiol* 1993; **36**: 391–9

39 Trophilme C, Becker AM, Jaffard HP, Jaulin P. Recherche d'anticorps irreguliers. Etude comparative sur 2 series de 20,000 sujets, l'une avec identification en technique tube, l'autre en gel-test. [English summary] *Transfus Clin Biol* 1995; **2**: 189–99

40 Heddle NM, Soutar RL, O'Hoski PL, et *al.* A prospective study to determine the frequency and clinical significance of alloimmunization post-transfusion. *Br J Haematol* 1995; **91**: 1000–5

41 Magovern JA, Sakert T, Benckart DH, et *al.* A model for predicting transfusion after coronary artery bypass grafting. *Ann Thorac Surg* 1996; **61**: 27–32

42 Owens WD, Felts JA, Spitznagel EL. ASA Physical status classifications: a study of consistency for rating. *Anesthesiology* 1978; **49**: 239–43

43 Wilson ME, Williams NB, Baskett PJF, et *al.* Assessment of fitness for surgical procedures and the variability of anaesthesists' judgement. *Br Med J* 1980; **280**: 509

44 Fawcus S, McIntyre J, Jewkes RK, et *al.* Management of incomplete abortions at South African public hospitals. National Incomplete Abortion Study Reference Group. *S Afr Med J* 1997; **87**: 438–42

45 Warner DO, Warner MA, Schroeder DR, Offord KP, Maxson P, Santrach P. Changing transfusion practices in hip and knee arthroplasty. *Transfusion* 1998; **38**: 738–44

46 Sculco TP, Gallina J. Blood management experience: relationship between autologous blood donation and transfusion in orthopedic surgery. *Orthopedics* 1999; **22**: s129–34

47 Grosflam JM, Wright EA, Cleary PD, Katz JN. Predictors of blood loss during total hip replacement surgery. *Arthritis Care Res* 1995; **8**: 167–73

48 Weber RS. A model for predicting transfusion requirements in head and neck surgery. *Laryngoscope* 1995; **105**: 1–17

49 Ransom SB, McNeeley SG, Malone-JM J. A cost-effectiveness evaluation of preoperative type-and-screen testing for vaginal hysterectomy. *Am J Obstet Gynecol* 1996; **175**: 1201–3

50 Ziekenfondsraad. *Diagnostisch kompas 1999/2000.* Ziekenfondsraad, The Netherlands, 1999. [Dutch]

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LABORATORY INVESTIGATIONS

Isoflurane-induced protection against myocardial stunning is independent of adenosine 1 (A_1) receptor in isolated rat heart

L. Yao*, R. Kato and P. Foëx

Nuffield Department of Anaesthetics, Oxford University, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

Corresponding author: Department of Anesthesiology, Tang Du Hospital, The Fourth Military Medical University, Xi'an 710038, China

Volatile anaesthetics can pharmacologically enhance the recovery of stunned myocardium, but the mechanism is still unknown. This study sought to determine whether isoflurane attenuates myocardial stunning, and whether the myocardial protection of isoflurane is mediated by adenosine A_1 receptors. Five groups (n=8) of isolated rat hearts were studied in the Langendorff apparatus. The control groups underwent 20-min ischaemia with or without adenosine receptor antagonist (DPCPX, A_1selective) treatment (Cont group and DPCPX group). In the isoflurane groups, isoflurane (1.5 MAC) was present throughout the experiment (Iso group) and DPCPX (200 nM) was administered from 10 min before ischaemia (Iso+DPCPX(pre-I) group) or the beginning of reperfusion (Iso+DPCPX(post-I) group) to the end of experiment. The isoflurane groups had a lower end-diastolic pressure than the control groups (P<0.05). Developed pressure recovered to 77, 76, and 82% in Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) groups, respectively (P<0.05 compared with control groups). LV+dp/dt$_{max}$ recovered to 53, 86, 81, 84, and 60% of pre-ischaemic values in Cont, Iso, Iso+DPCPX(pre-I), Iso+DPCPX(post-I), and DPCPX groups. LV-dp/dt$_{min}$ recovered to 55, 84, 83, 81, and 62%, respectively. Both LV+dp/dt$_{max}$ and LV-dp/dt$_{min}$ were significantly different (P<0.05) between control and isoflurane groups during reperfusion. There were no significant differences among the isoflurane groups. Our data show that isoflurane enhances the post-ischaemic functional recovery of isolated rat heart and that block of A_1 receptors does not abolish the beneficial effects of isoflurane. We conclude that A_1receptors are not involved in isoflurane-induced myocardial protection in the isolated rat heart.

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Myocardial stunning is the mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow.[1] Recently, the protective role of inhalation anaesthetic agents on the stunned myocardium has been studied in a number of animal models. After short periods of acute ischaemia, recovery of myocardial contractile function is more complete in animals anaesthetized with halothane or isoflurane than in awake animals.[2–5] Volatile anaesthetics can pharmacologically enhance the recovery of stunned myocardium, but the mechanism is still unknown.[6]

The protective effects of potent inhalation anaesthetics on myocardial stunning may be attributed to free radical scavenging, preservation of energy levels, and calcium channel block.[7] However, several inhalation anaesthetics were recently shown to have direct cardioprotective effects that mimic ischaemic preconditioning.[8–13] There is increasing evidence indicating that the end-effector mediating ischaemic preconditioning is the ATP-sensitive potassium channel (K_{ATP}).[14] Kersten and colleagues demonstrated that the improved mechanical function afforded by isoflurane was partially blocked by glibenclamide.[15] In a subsequent study, isoflurane-induced myocardial protection was shown

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to been partially mediated by adenosine type-1 receptor (A_1) activation.[16] Ismaeil and colleagues also found that 8-(*p*-sulfophenyl)-theophylline (SPT, an adenosine receptor antagonist) pre-treatment eliminated the preconditioning-like effect of isoflurane.[17] However, the signal transduction cascade responsible for isoflurane-induced myocardial protection has not been completely defined. Ismaeil speculated that isoflurane-induced preconditioning and ischaemia-induced preconditioning share similar mechanisms, which include activation of K_{ATP} channels and adenosine receptors.

There are three adenosine receptor subtypes in the cardiovascular system: A_1, A_2, and A_3.[18] Although ischaemic preconditioning in several species can be mimicked pharmacologically by selective adenosine A_1 or A_3 receptor agonists, it is currently unclear which receptor subtype is physiologically involved in mediating ischaemic preconditioning. The specific adenosine receptor subtypes involved in isoflurane-induced preconditioning also remain to be determined.

The purpose of this study was to identify whether isoflurane attenuates myocardial stunning induced by 20-min global ischaemia and if so, whether the myocardial protection of isoflurane is mediated by adenosine A_1 receptors. In addition, we compared the effects of A_1 receptor block given pre-ischaemia or post-reperfusion. A highly selective adenosine receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX), was used to block the A_1 receptor.

Materials and methods

The study was performed in accordance with the United Kingdom Animal Act (Scientific Procedures) 1986 (Home Office Project Licence number: PPL30/1496).

Isolated heart preparation

Adult male Wistar rats (325–350 g) were anaesthetized with an intraperitoneal injection of sodium pentobarbital 60 mg kg^{-1} and heparinized with 200 IU. The hearts were rapidly removed through a median sternotomy by transsecting all the major vessels, and arrested in ice-cooled Krebs–Henseleit buffer, then perfused retrogradely through the aorta in a non-recirculating Langendorff apparatus. The Krebs–Henseleit perfusion solution contained (mM) NaCl 118.7, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 0.95, $NaHCO_3$ 28, $CaCl_2$ 1.3, and glucose 10. The buffer was filtered through a 5.0 μm filter, equilibrated with a mixture of 95% oxygen and 5% carbon dioxide, had a pH 7.4, and was maintained at 37°C throughout the procedure. A fluid-filled polyethylene balloon was inserted through the mitral valve into the left ventricle and connected by a polyethylene catheter to a saline-filled syringe and to a pressure transducer (Medex Medical Inc, Lancashire, UK). The volume of the balloon was adjusted to achieve an end-diastolic pressure (EDP) of 5–8 mm Hg, which remained unchanged throughout the experiment. All hearts were paced with right ventricular epicardial electrodes at a fixed rate of 300 beats min^{-1} (2 ms, 5 V). Perfusion pressure was set at 100 cmH_2O and maintained constant. Myocardial temperature was maintained at 37°C by submersing the heart into a water-jacketed chamber filled with Krebs–Henseleit buffer. A three-way stopcock placed above the aortic root was positioned to stop flow and, thus, produce global ischaemia. Electric pacing was stopped during ischaemic periods and resumed 2 min after reperfusion. Hearts were defibrillated when necessary.

Experimental design

All experiments lasted 150 min beginning with a 10-min period of stabilizing perfusion for equilibration. Forty rats were assigned randomly to one of the following five groups (n=8). The hearts in the control groups underwent 20-min ischaemia with or without DPCPX (200 nM) treatment (Cont group and DPCPX group). In the isoflurane groups, isoflurane (1.5 MAC) was present throughout the experiment except during the ischaemic period (Iso group). In addition, DPCPX (200 nM) was administered for 10 min before ischaemia and during reperfusion in the Iso+DPCPX(pre-I) group, and only during reperfusion in the Iso+DPCPX(post-I) group. Reperfusion lasted for 120 min in all groups. Isoflurane was administered by placing an isoflurane vaporizer between the fresh gas supply and the perfusate. A gas analyser (M1025A, Hewlett Packard, San Francisco, CA, USA) continuously monitored the delivered vapour concentration. As the MAC of isoflurane in rats was 1.5%[19] a concentration of 2.25% was used to obtain 1.5 MAC. DPCPX (ICN Biomedicals Inc., Aurora, Ohio, USA) was first dissolved in DMSO (dimethylsulphoxide, Sigma-Aldrich, Dorset, UK) and then the perfusate so that the final concentrations of DPCPX and DMSO in the perfusate were 200 nM and 0.025%, respectively.

Data collection and analysis

Left ventricular pressure was monitored continuously throughout the experiment. The left ventricular pressure signal was digitized at 100 Hz (analogue-digital converter AT-MIO, National Instruments Corporation, TX, USA) and stored on the hard disk of a desktop computer. Peak left ventricular pressure (PSP), developed pressure (end-systolic minus end-diastolic, DP), end-diastolic pressure (EDP) and positive and negative LVdp/dt were obtained and processed using data acquisition and analysis software developed in our department. After a period of stabilization (10 min), ventricular mechanical function was measured as a baseline, then measurements were obtained at the following time points: just before the onset of ischaemia, 10, 20, 30, 60, 90, and 120 min after reperfusion.

Table 1 Indices of mechanical function before global ischaemia in group Cont, Iso, Iso+DPCPX(pre-I), Iso+DPCPX(post-I) and DPCPX. DP=developed pressure; EDP=end-diastolic pressure; +dp/dt=maximum positive left ventricular pressure derivative; –dp/dt=minimum negative left ventricular pressure derivative. Results are mean (SEM), $^{*}P<0.05$ compared with group Cont and DPCPX

Group	DP (mm Hg)		EDP (mm Hg)		+dp/dt(mm Hg s^{-1})		–dp/dt (mm Hg s^{-1})	
	Baseline	**Pre-I**	**Baseline**	**Pre-I**	**Baseline**	**Pre-I**	**Baseline**	**Pre-I**
Cont	111(2)	108(2)	5(0)	5(0)	2497(64)	2394(77)	1685(56)	1707(85)
Iso	109(3)	89(4)*	6(0)	5(1)	2533(43)	1850(23)*	1661(86)	1338(47)*
Iso+DPCPX(pre-I)	110(2)	87(1)*	5(0)	10(2)*	2496(70)	1849(98)*	1771(39)	1278(68)*
Iso+DPCPX(post-I)	114(2)	86(1)*	5(0)	6(1)	2627(41)	1907(21)*	1862(21)	1375(21)*
DPCPX	114(3)	110(3)	6(0)	6(0)	2675(68)	2504(81)	1885(41)	1786(37)

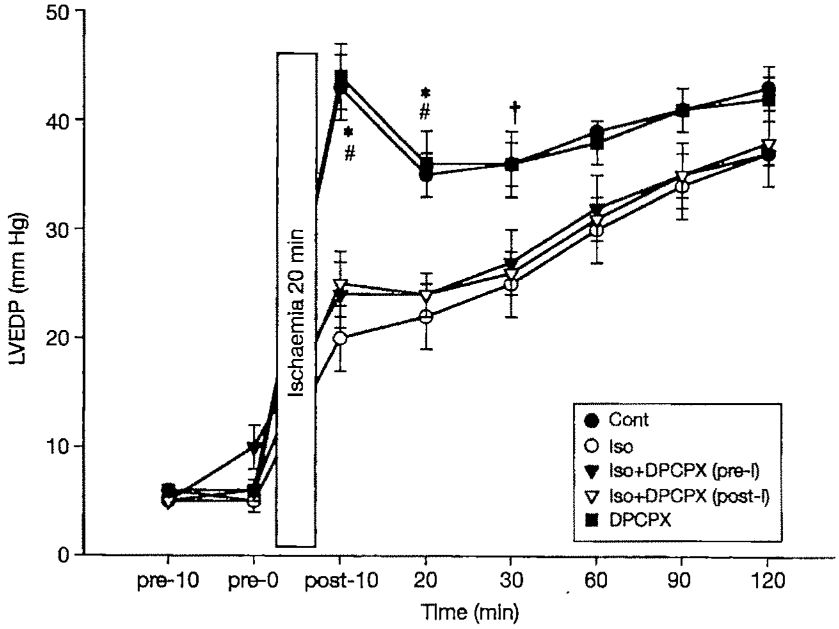

Fig 1 Changes of EDP before and after global ischaemia in rats. Values are expressed as mean (SEM). $^{*}P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with Cont group. $^{\#}P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with DPCPX group. $^{\dagger}P<0.05$ Iso group compared with Cont group.

Statistical analysis

All values are expressed as mean (SEM). After ischaemia, DP, LV+dp/dt_{max}, and LV–dp/dt_{min} are expressed as the percentage of the values before ischaemia. Before ischaemia and during reperfusion differences in indices among groups were compared using two-way analysis of variance (ANOVA) for treatment and time with repeated measures on a time factor. If ANOVA indicated significant difference between groups, further comparisons on specific times were performed using one-way ANOVA followed by Bonferroni's post-hoc test. Statistical significance was assumed at $P<0.05$. All analyses were performed using the SPSS 10.0 software system under Windows 98 operating system.

Results

Contractile and diastolic function before myocardial ischaemia

The data on mechanical function before ischaemia is shown in Table 1. After 10 min equilibration, left ventricular DP, EDP, LV+dp/dt_{max} and LV–dp/dt_{min} were similar among the groups under baseline conditions. Isoflurane at 1.5 MAC significantly decreased DP, LV+dp/dt_{max} and LV–dp/dt_{min} before ischaemia compared with Cont group and DPCPX group ($P<0.05$). DPCPX did not alter the effects of isoflurane on DP, LV+dp/dt_{max} and LV–dp/dt_{min} in the Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group, but the EDP in Iso+DPCPX(pre-I) group was higher than in the other groups ($P<0.05$).

Contractile and diastolic function after myocardial ischaemia

Ischaemia induced a significant increase in EDP in all groups, but the isoflurane groups (isoflurane with or without DPCPX) had a lower EDP than the control groups ($P<0.05$). There was no significant difference in EDP among the isoflurane groups at the end of 20 min of ischaemia. After 30 min of reperfusion, EDP in all groups increased and the only significant difference was between Iso and Conts group (Fig. 1). Figure 2 shows the recovery of DP during 120 min

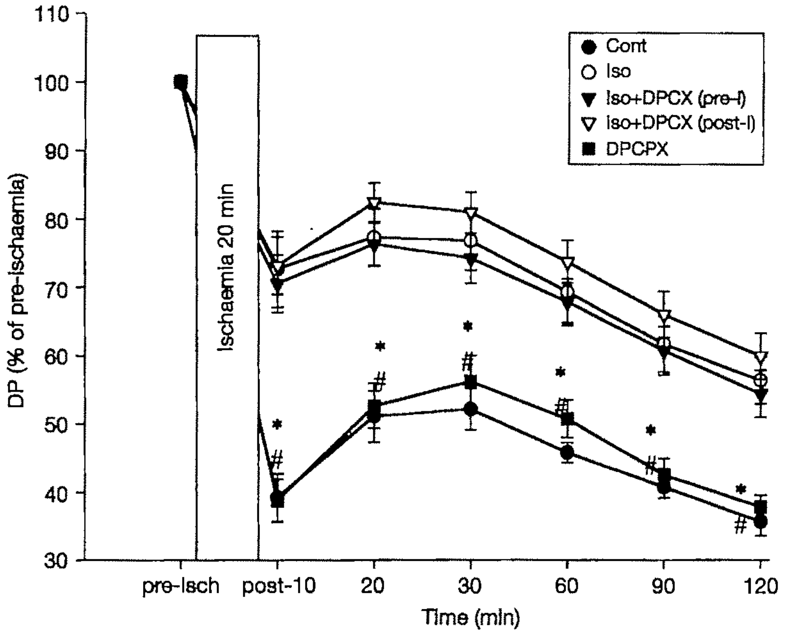

Fig 2 Post-ischaemic recovery of left ventricular developed pressure in rats. Values are expressed as a per cent of pre-ischaemic values (mean (SEM)). *$P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with Cont group. $^{\#}P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with DPCPX group.

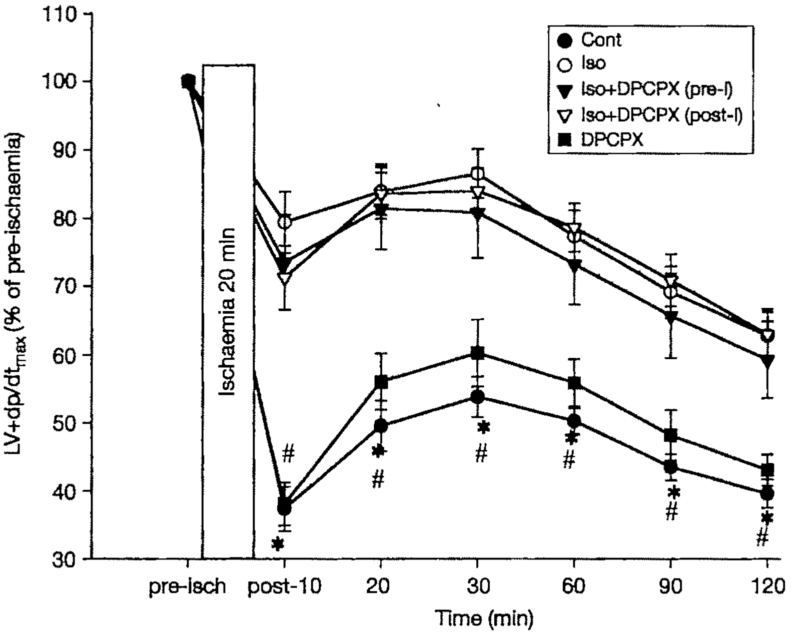

Fig 3 Post-ischaemic recovery of maximum positive left ventricular pressure derivative in rats. Values are expressed as a per cent of pre-ischaemic values (mean (SEM)). *$P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with Cont group. $^{\#}P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with DPCPX group.

of reperfusion. In the Cont and DPCPX groups, DP recovered to 52 and 53% of pre-ischaemic values and was significantly different from the Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) groups (77, 76, and 82%, respectively; $P<0.05$). No significant difference in DP was found among the isoflurane groups and between Cont and DPCPX group. At 30 min of reperfusion, DP attained maximum recovery in all groups, and then decreased gradually, but a significant difference between control and isoflurane groups persisted (Fig. 2).

Figure 3 shows the recovery of LV+dp/dt$_{max}$ during reperfusion. The changes of LV+dp/dt$_{max}$ were similar to those of developed pressure. In the Cont, Iso, Iso+DPCPX(pre-I), Iso+DPCPX(post-I), and DPCPX

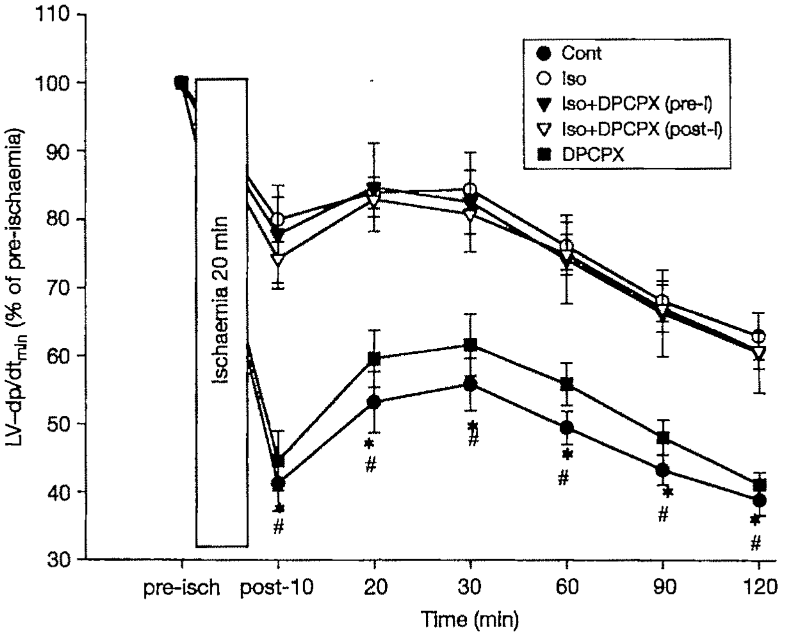

Fig 4 Post-ischaemic recovery of minimum negative left ventricular pressure derivative in rats. Values are expressed as a per cent of pre-ischaemic values (mean (SEM)). *$P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with Cont group. $^{\#}P<0.05$ Iso, Iso+DPCPX(pre-I) and Iso+DPCPX(post-I) group compared with DPCPX group.

groups, LV+dp/dt$_{max}$ was 1280 (SEM 62), 1603 (74), 1457 (68), 1601 (60), and 1498 (62) mm Hg s^{-1}, respectively, and recovered to 53, 86, 81, 84, and 60% of pre-ischaemic values at 30 min of reperfusion. There was a significant difference ($P<0.05$) between control and isoflurane groups at every time point during reperfusion (Fig. 3). Similar findings were obtained for LV–dp/dt$_{min}$ (Fig. 4). LV–dp/dt$_{min}$ also achieved maximum recovery at the 30 min reperfusion and reached 55, 84, 83, 81, and 62% in Cont, Iso, Iso+DPCPX(pre-I), Iso+DPCPX(post-I), and DPCPX groups, respectively ($P<0.05$ compared with control groups). At the end of reperfusion, the percentages of LV-dp/dt$_{min}$ recovery were 39, 63, 60, 61, and 41%, respectively. There was no significant difference in LV–dp/dt$_{min}$ among isoflurane groups, but there was a significant difference between the control and isoflurane groups.

Discussion

These results indicate that exposure to isoflurane before and after an ischaemic insult improves recovery of mechanical function and DPCPX, an adenosine A_1 receptor antagonist, does not abolish the beneficial effects of isoflurane, whether administered before or after ischaemia in the isolated rat heart.

Many studies indicate that volatile anaesthetics protect the myocardium after global or regional ischaemia, in models of reversible and irreversible tissue injury.[2–5 20 21] Recent findings suggest that isoflurane modulates cardioprotection via a signal transduction mechanism similar to the endogenous mechanism that mediates ischaemic preconditioning, for example, through activation of adenosine A_1 receptor coupled to K_{ATP} channels.[9 10 14–17] Indeed, Kersten and colleagues found that isoflurane directly preconditions the myocardium via activation of K_{ATP} channels, confirming and extending previous studies.[9]

The preconditioning protection observed with brief ischaemia seems to be mediated by the release of adenosine. Adenosine binds to its receptors (A_1 and possibly A_3), and, via a G-protein-linked process, increases protein kinase C (PKC) activity.[22] However, the role of adenosine receptors in the modulation of the cardioprotective signal transduction during isoflurane anaesthesia has not been completely identified. Kersten showed that the cardioprotective effects of isoflurane were attenuated by pre-treatment with DPCPX in dogs[16] and DPCPX, a xanthine derivative, has been shown to be 700-fold more selective for A_1 than for A_2 receptors in radioligand binding studies and *in vitro* functional assays.[23] These data indicated that isoflurane-induced myocardial protection is partially mediated by A_1 receptor activation. Ismaeil and colleagues found that SPT, a non-specific adenosine receptor antagonist, could block the preconditioning-like effect of isoflurane in propofol-anaesthetized rabbits; SPT returned infarct size to values comparable with those in the control group.[17] Previously, Cope and co-workers demonstrated that halothane, enflurane, and isoflurane protect the heart from infarction. They also found that myocardial protection by halothane was abolished by SPT *in vitro* in the rabbit heart.[20] It seems that isoflurane-induced preconditioning shares some of the same fundamental underlying mechanisms as ischaemia-induced preconditioning. That is the activation of adenosine A_1

receptors followed by the opening of K_{ATP} through protein kinase C (PKC). However, in our study, DPCPX did not block or attenuate isoflurane-induced myocardial protection.

How can the differences between this and previous studies in respect of DPCPX be explained?

First, the animal model may be an important factor. We used the model of the isolated buffer-perfused rat heart to investigate direct effects of isoflurane on myocardial ischaemia/reperfusion injury. Compared with *in vivo* studies, that identified the role of adenosine receptors in isoflurane-induced myocardial protection, our model excludes several effects of isoflurane that may be important in the *in vivo* situation of ischaemia and reperfusion, such as haemodynamic and humoral effects, sympathetic nervous system activity, or activation of neutrophils.[24 25] Furthermore, the species difference should also be considered. It has been found that adenosine A_1 receptor activation did not appear to be involved in ischaemic preconditioning in the rat, although it has been implicated in the rabbit, the dog, and the pig. In isolated working rat hearts, Cave and colleagues found that a 5-min period of perfusion with adenosine (10, 50, and 100 μM) followed by a 5-min adenosine-free perfusion period failed to increase the recovery of function after a subsequent 20-min period of global ischaemia.[26]

Second, the concentration of DPCPX used in the present study was 200 nM according to previous experiments. To determine whether the concentration of DPCPX at 200 nM was enough to block the adenosine A_1 receptor in rat heart, Hara and co-workers examined the effects of DPCPX (100 nM) on the negative chronotropic action induced by a high concentration of adenosine (50 μM).[27] The results showed that DPCPX completely prevented the decrease in heart rate. Therefore, concentration of DPCPX used in our study has the ability to block the adenosine A_1 receptors. In Kersten's study, which showed that isoflurane-induced myocardial protection of stunned myocardium is partially mediated by A_1 receptor activation, the dosage of DPCPX was 0.8 mg kg^{-1}. But Yao and co-workers previously demonstrated that a higher dose of DPCPX (1 mg kg^{-1}, intravenously) exacerbated myocardial stunning and caused significantly greater reduction in %SS during reperfusion when compared with dogs receiving the drug vehicle alone.[28]

Third, although it is well established that adenosine A_1 receptor activation preconditions the heart against infarction, it remains controversial whether A_1 receptor activation can also precondition against stunning. Studies using multiple 5-min coronary occlusions interspersed with 10 min of reperfusion have yielded conflicting results, with one study suggesting that adenosine receptor block prevents the preconditioning effects of the first occlusion and another suggesting that it does not.[28 29] The mechanism of stunning may be different from myocardial infarction; adenosine receptors could be important in infarction, but we cannot necessarily implicate them in myocardial stunning.

A number of hypotheses regarding the mechanism of myocardial stunning have been proposed since the 1980s, most of which have been subsequently abandoned. At present, the two favoured theories regarding the pathogenesis of myocardial stunning are the oxyradical hypothesis and the calcium hypothesis.[30] Volatile anaesthetics have been shown to affect free radical activity. Tanguay and colleagues showed a beneficial effect of halothane, isoflurane, and enflurane on free radical-induced impairment of cardiac function in isolated rabbit hearts. Halothane completely inhibited the initial burst of hydroxyl production during early reperfusion.[31] However, the effects of anaesthetics on free radicals are inconclusive. On the other hand, volatile anaesthetics affect Ca^{2+} movements during the cardiac cycle. Ca^{2+} flux into and out of the heart cell is mediated primarily by Ca^{2+} channels and the Na^+/Ca^{2+} exchanger. Haworth and colleagues found that halothane, isoflurane, and enflurane inhibit both Na^+/Ca^{2+} exchange and Ca^{2+} channels at concentrations relevant to anaesthesia, although they exhibit differences in potency and number of sites of action. At 1.5 MAC, halothane inhibits Ca^{2+} channels more than Na^+/Ca^{2+} exchange, whereas enflurane inhibits Na^+/Ca^{2+} exchange more than Ca^{2+} channels. Isoflurane inhibits both systems equally.[32] The negative inotropic effect of isoflurane on rat papillary muscle has been investigated by Lynch and Frazer,[33] suggesting isoflurane also affects Ca^{2+} channels in the rats.

The observation that there is an initial recovery of function immediately after reperfusion, followed by a subsequent decline at 30 min, supports the occurrence of additional injury in the initial phase of reflow. Both free radicals and calcium overload may contribute to this phenomenon. Accordingly, the better functional recovery in the isoflurane groups compared with control group could be ascribed to the inhibition of the production of free radicals or the prevention of calcium overload by isoflurane. Furthermore, physiological studies of the mechanism of stunning point to a lesion at the level of the myofilaments. Toda found that isoflurane increased submaximum Ca^{2+} activated force development of the contractile proteins in skinned rabbit femoral arterial strips.[34] This isoflurane-induced increase in force is blocked by inhibition of Ca^{2+}-independent PKC and suggests that isoflurane may increase the activity of ε-PKC, a prominent calcium-independent PKC isoform and one that has been implicated as a critical mediator of ischaemic preconditioning. Thus, we can speculate that PKC is also involved in the isoflurane-induced myocardial protection. Although such a hypothesis may be highly plausible, direct evidence of activation of any specific PKC isoform by isoflurane has yet to be demonstrated and would represent an important goal of future research.

It has been proposed that the injury responsible for myocardial stunning consists of ischaemic and reperfusion injury, with reperfusion injury respresenting the larger component. However, at the same time, ischaemic injury and reperfusion injury are not independent entities; any intervention that attenuates the severity of the ischaemic injury, such as adenosine, calcium antagonists, K_{ATP} channel openers, will also, indirectly, attenuate the severity of the subsequent reperfusion injury.[30] The primary aim of administration of DPCPX to the perfusate before and after ischaemia was to investigate the potentially different role of A_1 receptor in ischaemic *vs* reperfusion injury. We found that the adenosine receptor antagonist, DPCPX, does not abolish the beneficial effects of isoflurane, whether administered before or after ischaemia. This indicates that A_1 receptors are not involved in the isoflurane-induced myocardial protection, vis-à-vis ischaemic injury or reperfusion injury.

We cannot completely rule out that better recovery of DP, LV+dp/dt$_{max}$, LV−dp/dt$_{min}$ and EDP during reperfusion resulted from the effect of isoflurane on myocardial metabolism. However, Mattheussen and co-workers found that depressed cardiac function during exposure to halothane and isoflurane did not correlate with myocardial ATP content, suggesting that ATP metabolism during ischaemia was not influenced by halothane or isoflurane.[35]

Myocardial protection should be considered in a variety of clinical settings such as thrombolysis, percutaneous balloon angioplasty and after periods of cardiac arrest during cardiac surgery with cardiopulmonary bypass. If clinical investigations could show that isoflurane protects against myocardial stunning, this may influence the choice of anaesthetic agent for cardiac surgery.

In conclusion, our results show that isoflurane enhances the post-ischaemic functional recovery of the isolated rat heart undergoing 20 min ischaemia when used throughout the experiment. Block of A_1 receptors whether before or after ischaemia does not abolish the beneficial effects of isoflurane. We conclude that A_1 receptors in rat heart are not involved in the processes of isoflurane-induced myocardial protection, in either the ischaemic or reperfusion phases.

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References

1 Ambrosio G. Preserved high energy phosphate metabolic reserve in globally stunned hearts despite reduction of basal ATP content and contractility. *J Mol Cell Cardiol* 1987; **19**: 953–64

2 Warltier DC, Al-Wathiki MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552–65

3 Kanaya N, Kobayashi I, Nakayama M, Fujita S, Namiki A. ATP sparing effect of isoflurane during ischaemia and reperfusion of the canine heart. *Br J Anaesth* 1995; **74**: 563–8

4 White JL, Myers AK, Analouei, Kim YD. Functional recovery of stunned myocardium is greater with halothane than fentanyl anaesthesia in dogs. *Br J Anaesth* 1994; **73**: 214–9

5 Gross GJ, Kersten JR, Warltier DC. Mechanisms of postischemic contractile dysfunction. *Ann Thorac Surg* 1999; **68**: 1898–904

6 Coetzee A, Skein W, Genade S, Lochner A. Enflurane and isoflurane reduce reperfusion dysfunction in the isolated rat heart. *Anesth Analg* 1993; **76**: 602–8

7 Ross S, Foëx P. Protective effects of anaesthetics in reversible and irreversible ischaemia-reperfusion injury. *Br J Anaesth* 1999; **82**: 622–32

8 Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. Mechanism of myocardial protection by isoflurane. Role of adenosine triphosphate-regulated potassium (K_{ATP}) channels. *Anesthesiology* 1996; **85**: 794–807

9 Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC. Isoflurane mimics ischemic preconditioning via activation of K_{ATP} channels. *Anesthesiology* 1997; **87**: 361–70

10 Toller W, Montgomery MW, Pagel PS, Hettrick DA, Warltier DC, Kersten JR. Isoflurane-enhanced recovery of canine stunned myocardium. *Anesthesiology* 1999; **91**: 13–22

11 Boutros A, Wang J, Capuano C. Isoflurane and halothane increase adenosine triphosphate preservation, but do not provide additive recovery of function after ischemia, in preconditioned rat hearts. *Anesthesiology* 1997; **86**: 109–17

12 Novalija E, Fujita S, Kampine JP, Stowe DF. Sevoflurane mimics ischemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. *Anesthesiology* 1999; **91**: 701–12

13 Hawaleshka A, Jacobsohn E. Ischemic preconditioning: mechanisms and potential clinical applications. *Can J Anaesth* 1998; **45**: 670–82

14 Kersten JR, Pagel PS, Gross GJ, Warltier DC. Activation of adenosine triphosphate-regulated potassium channels. *Anesthesiology* 1998; **88**: 495–513

15 Kersten JR, Lowe D, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. Glyburide, a K_{ATP} channel antagonist, attenuates the cardioprotective effects of isoflurane in stunned myocardium. *Anesth Analg* 1996; **83**: 27–33

16 Kersten JR, Orth KG, Pagel PS, Mei DA, Gross GJ, Warltier DC. Role of adenosine in isoflurane-induced cardioprotection. *Anesthesiology* 1997; **86**: 1128–39

17 Ismaeil MS, Tkachenko I, Gamperl AK, Hickey RF, Cason BA. Mechanisms of isoflurane-induced myocardial preconditioning in rabbits. *Anesthesiology* 1999; **90**: 812–21

18 Hill R, Oleynek J, Hoth C. Cloning expression and pharmacological characterization of rabbit adenosine A_1 and A_3 receptors. *J Pharmacol Exp Ther* 1997; **280**: 122–8

19 Mazze RI, Rice SA, Baden JM. Halothane, isoflurane and enflurane MAC in pregnant and nonpregnant female and male mice and rats. *Anesthesiology* 1985; **62**: 339–41

20 Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anaesthetics protect the ischemic rabbit myocardium from infarction. *Anesthesiology* 1997; **86**: 699–709

21 Cason BA, Gamperl AK, Slocum RE, Hickey RF. Anesthetics-induced preconditioning. Previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* 1997; **87**: 1182–90

22 Lynch C III. Anesthetic preconditioning, not just for heart. *Anesthesiology* 1999; **91**: 606–8

23 Lohse MJ, Klotz KN, Lindenborn-Fotions J, Reddington M, Schwabe U, Olsson RA. 8-Cyclopentyl-1, 3-dipropylxanthine (DPCPX) – a selective high affinity antagonist radioligand for A_1

adenosine receptors. *Naunyn-Schmiedebergs Arch Pharmacol* 1987; **336**: 204–10

24 Lynch C III. Differential depression of myocardial contractility by halothane and isoflurane *in vivo*. *Anesthesiology* 1986; **64**: 620–31

25 Kovalski C, Zahler S, Becker BF. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997; **86**: 188–95

26 Cave A, Collins C, Downey J, Hearse D. Improved functional recovery by ischaemic preconditioning is not mediated by adenosine in the globally ischaemic rat heart. *Cardiovasc Res* 1993; **27**: 663–8

27 Hara A, Abiko Y. Protective effects of hypoxia on mechanical and metabolic changes induced by hydrogen peroxide in rat hearts. *Am J Physiol* 1995; **268**: H614–20

28 Yao Z, Gross GJ. Glibenclamide antagonizes adenosine A_1 receptor-mediated cardioprotection in stunned canine myocardium. *Circulation* 1993; **88**: 235–44

29 Bunch FT, Thornton J, Cohen MV, Downey JM. Adenosine is an endogenous protectant against stunning during repetitive ischemic episodes in the heart. *Am Heart J* 1992; **124**: 1440–6

30 Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev* 1999; **70**: 609–63

31 Tanguay M, Blaise G, Dumont L, Belque G, Hollman C. Beneficial effects of volatile anaesthetics on decrease in coronary flow and myocardial contractility induced by oxygen-derived free radicals in isolated rabbit hearts. *J Cardiovasc Pharmacol* 1991; **18**: 863–70

32 Haworth RA, Coknur AB. Inhibition of sodium/calcium exchange and calcium channels of heart cells by volatile anaesthetics. *Anesthesiology* 1995; **82**: 1255–65

33 Lynch C III, Frazer MJ. Depressant effects of volatile anesthetics upon rat and amphibian ventricular myocardium: insights into anesthetic mechanism of action. *Anesthesiology* 1989; **70**: 511–22

34 Toda H, Su JY. Mechanism of isoflurane-induced submaximum Ca^{2+}-activated force in rabbit skinned femoral arterial strips. *Anesthesiology* 1998; **89**: 731–40

35 Mattheussen M, Rusy BF, Aken HV, Flameng W. Recovery of function and adenosine triphosphate metabolism following myocardial ischemia induced in the presence of volatile anesthetics. *Anesth Analg* 1993; **76**: 69–75

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Aerosolized surfactant therapy for endotoxin-induced experimental acute respiratory distress syndrome in rats

K. Tashiro[1]*, K. Yamada[1], T. Konzaki[1], K. Yamamoto[1], S. Ohmura[1], T. Kobayashi[1] and Y. Suzuki[2]

[1]*Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan.* [2]*Department of Ultrastructural Research, Institute for Frontier Medical Sciences, Kyoto University, Japan*

**Corresponding author*

We have compared the effects of inhalation of aerosolized surfactant on experimental acute respiratory distress syndrome. *Escherichia coli* endotoxin (55 (SD 20) mg kg^{-1}) was injected into the tracheas of 36 adult rats anaesthetized and mechanically ventilated with pure oxygen. When the Pa_{O_2} decreased to 11.3 (3.3) kPa, the animals were randomly subjected to inhalation of aerosolized modified natural surfactant (MNS) for 0 min (control group), 30, 60, and 120 min. In the control group, Pa_{O_2} remained below 12 kPa for 180 min. In the groups receiving inhalation of surfactant for 30 and 60 min, Pa_{O_2} increased but decreased soon after termination of the inhalation. In contrast, Pa_{O_2} of the group receiving inhalation of surfactant for 120 min continued to increase, reaching 52.1 (12.5) kPa at 180 min ($P<0.05$ *vs* control). Thus, we conclude that improvement in gas exchange as a result of inhalation of MNS depends on the duration of inhalation.

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Pulmonary surfactant, consisting of phospholipids and surfactant-associated proteins (SPs); SP-A (hydrophilic), SP-B (hydrophobic), SP-C (hydrophobic), and SP-D (hydrophilic),[1 2] prevents atelectasis and lung oedema by reducing surface tension of the alveoli.[2 3] In acute respiratory distress syndrome (ARDS), various surfactant inhibitors appear in the alveolar space.[4 5] Surfactant replacement therapy has been tried in patients with ARDS to restore surfactant function,[6–8] resulting in short-term improvement in gas exchange.[7 8] The replacement technique with bolus intra-tracheal instillation may present difficulties for early treatment of ARDS, as it may cause circulatory instability.[9 10] On the other hand, inhalation of aerosolized surfactant can be used for such patients, as this procedure did not change arterial pressure in our previous study using rats with experimental ARDS caused by endotoxin.[10] We found, however, that the therapeutic effects of inhalation of aerosolized surfactant for 60 min were inferior to those of intra-tracheal instillation of surfactant (100 mg kg^{-1}). In the present study, we examined whether prolonged inhalation of aerosolized surfactant can improve Pa_{O_2} in the same experimental ARDS model.

Methods

Preparation of surfactant

A modified natural surfactant (MNS) was isolated from the lungs of recently slaughtered pigs. The alveolar lavage fluid was centrifuged at 150 *g* for 10 min to remove cell debris. The supernatant was further centrifuged at 2000 *g* for 60 min to obtain pellets of crude surfactant. This crude surfactant was purified by extraction with chloroform-methanol (2:1, v:v) and acetone precipitation.[11] This surfactant consisted of 98% phospholipids (by weight), 1% other lipids, and 1% hydrophobic SPs (SP-B and SP-C).[11] It was reported that this MNS was effective for treatment of babies suffering from respiratory distress syndrome[12] and that it increased lung compliance of immature newborn rabbit to a similar extent as a porcine surfactant obtained with liquid–gel chromatography.[13] This

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MNS was suspended in normal saline at a concentration of 25 mg ml^{-1}.

Main procedure

With the approval of the Animal Care Committee of the Kanazawa University School of Medicine, 36 male Wistar rats weighing between 320 and 440 g were anaesthetized with an i.p. injection of pentobarbital sodium (30 mg kg^{-1}), and the lungs intubated through a tracheotomy. One femoral artery was cannulated to allow monitoring of arterial pressure and removal of blood samples. Lactated Ringer's solution containing a neuromuscular blocking agent (0.02 mg ml^{-1} pancuronium bromide) was continuously infused at a rate of 10 ml kg^{-1} h^{-1} through one femoral vein. Pentobarbital sodium (a single dose of 15 mg kg^{-1}) was injected into the peritoneal cavity when additional anaesthesia was necessary.

The experiment was always performed concurrently on three rats, which made up one set, each rat being connected in parallel to a pressure-controlled ventilator (Servo 900B, Siemens-Elema, Solna, Sweden) delivering 100% oxygen at a frequency of 40 breaths min^{-1} with an inspiration time of 50%, and a fixed peak inspiratory pressure of 25 cm H_2O. At the beginning of the experiment, the positive end-expiratory pressure (PEEP) was set at 7.5 cm H_2O with the aid of a variable resistor (E037E, Siemens-Elema). After registration of the baseline value for arterial blood gases, PEEP was reduced to 0 cm H_2O, and 40 mg kg^{-1} of endotoxin (*E. coli* O111:B4, Difco Laboratories, Detroit, MI, USA), suspended in normal saline (20 mg ml^{-1}), was injected into the lungs through the tracheal tube over 1 s. Arterial blood samples were analysed for Pa_{O_2} every 30 min. The same dose was re-administered to an individual rat whose Pa_{O_2} was higher than 53 kPa 30 min after the first injection.

All three rats in the set were ventilated with these ventilatory settings until Pa_{O_2} decreased to less than 27 kPa; this oxygen index value was chosen based on the criteria for ARDS patients.[14] Then, the PEEP was increased in increments of 2.5 cm H_2O. Sequences of increment in PEEP and ventilation were repeated until the Pa_{O_2} decreased to less than 27 kPa despite a PEEP of 7.5 cm H_2O. Then, lung oedema fluid in the airway was removed by tracheal suction with a fine catheter. When the Pa_{O_2} values of all three rats in a set remained at less than 27 kPa 15 min after tracheal suctioning, experimental ARDS was considered to be fully developed. One rat in the set was randomly assigned to a control group and did not receive any aerosol into the airway. The other two rats were randomly assigned to two of three aerosolized surfactant groups as described below.

Rats in the AS-30, AS-60, and AS-120 groups underwent inhalation of aerosolized MNS for 30, 60, and 120 min, respectively. For this purpose, the rats were connected to an inhalation circuit constructed as a branch circuit, to which the ventilator delivered oxygen under the same conditions as for the main circuit.[15] An ultrasonic nebulizer (NE-U06, Omron, Tokyo, Japan), with its blowing system shut off, was positioned 7 cm proximal to the tracheal tube. A 3-ml aliquot of the MNS suspension was placed in the reservoir of the nebulizer, which produced an aerosol (mean droplet diameter, 3.4 (SD 1.2) μm) by means of ultrasound (2.4 MHz, 30 W).[15] The moment when the aerosol inhalation was initiated was termed the 'starting point'. Another 3 ml of the fresh MNS suspension was added to the reservoir every 15 min. After completion of the inhalation, the rats were reconnected to the original ventilatory circuit. Arterial blood samples were then evaluated sequentially for Pa_{O_2}, Pa_{CO_2} and base excess (BE) using a conventional analyser (ABL-520, Radiometer, Copenhagen, Denmark) until 180 min after the starting point. Tracheal suction was performed 5 min before each blood gas analysis. A fixed volume of 0.5 ml of sodium bicarbonate (1 Eq litre^{-1}) was administered for correction of metabolic acidosis after each blood gas analysis if BE was lower than –5 mEq litre^{-1}

At the end of the experiment (i.e. 180 min after the starting point), a sublethal dose of pentobarbital was administered, after which the tracheal tube was plugged to cause absorption atelectasis followed by death. Next, the thorax was opened and all rats were connected in parallel to an apparatus for static pressure-volume recordings of the lung.[16] Airway pressure was raised in a stepwise manner from 0 to 30 cm H_2O, and then lowered, also in a stepwise manner, to 0 cm H_2O, with a 1-min period of stress relaxation at each 5-cm H_2O level. These volume measurements were corrected for gas compression.

Additional procedure

To assess the distribution of aerosolized MNS in the lungs, an additional experiment was performed on three pairs of lung-lavaged rats.[17] The rats were mechanically ventilated with a peak inspiratory pressure of 25 cm H_2O and a PEEP of 7.5 cm H_2O using pure oxygen, and underwent lung-lavage with normal saline (40 ml kg^{-1}, 37°C) six times. One rat of the pair was ventilated for 60 min without administration of any aerosolized MNS, while the other rat of the pair was subjected to inhalation of aerosolized MNS for 60 min in the same manner as described in the main procedure. Rats were then killed and their thorax opened. The lungs were expanded at an airway pressure of 10 cm H_2O, and were fixed by immersion of the whole body in a formalin solution (10%) for 3 h. The lungs were then removed and further fixed in formalin for several weeks.

Lung sections were examined for localization of SP-B with the aid of monoclonal mouse anti-SP-B antibody (8B5E).[18] This antibody binds with SP-B derived from both rat and pig so that both endogenous and exogenous

Table 1 Body weight, endotoxin dose, and rat mortality (mean (SD)). Elapsed time: time between the first injection of endotoxin and the starting point (=aerosol initiation)

Group	*n*	Body weight (g)	Endotoxin (mg kg^{-1})	Elapsed time (min)	Number of dead rats (mortality rate, %)
Control	12	375 (31)	53 (20)	184 (83)	5 (42)
AS-30	8	383 (32)	60 (21)	177 (81)	3 (38)
AS-60	8	378 (27)	55 (21)	191 (89)	2 (25)
AS-120	8	363 (17)	55 (21)	183 (85)	2 (25)

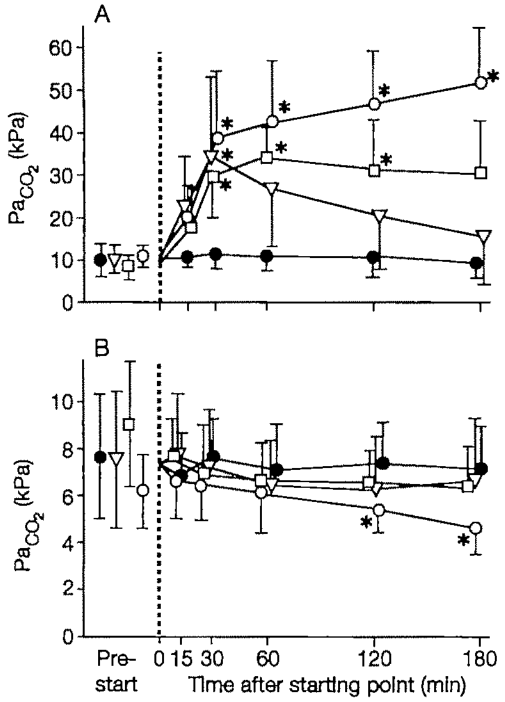

Fig 1 Pa_{O_2} (A) and Pa_{CO_2} (B) in rats injected with endotoxin. All rats were mechanically ventilated at a peak inspiratory pressure of 25 cm H_2O and a PEEP of 7.5 cm H_2O for the indicated times. AS-30 (open triangles, *n*=8), AS-60 (open boxes, *n*=8) and AS-120 (open circles, *n*=8) groups underwent inhalation of an aerosolized MNS for 30, 60, and 120 min, respectively, from the starting point. The control group (closed circles, *n*=12) did not received aerosol. Pre-start: pre-starting period. Values show means (SD). * $P<0.05$ *vs* the control group.

surfactants could be detected. In brief, the lung sections were first counterstained with Meyer's haematoxylin and intrinsic peroxidase activity was inhibited by means of 0.3% hydrogen peroxide in methanol for 30 min. Next, they were incubated with anti-SP-B antibody in phosphate-buffered saline (PBS) for 30 min after blocking non-specific binding sites with 5% bovine serum albumin in PBS. The sections were immersed in biotinylated anti-mouse IgG (H+L) (Vector Laboratories, Inc., Burlingame, CA, USA) and then in a solution of avidin-biotinylated horseradish peroxidase complex (VECTASTAIN ABC kit, Vector Laboratories). The final peroxidase reaction was performed with 0.05% diaminobenzidine-tetrahydrochloride and 0.01% hydrogen peroxide. The sections serving as controls were treated in the same manner but without primary antibody.

Statistical analysis

Data are presented as mean (SD). Differences in survival rates and the proportion of rats that needed second injections of endotoxin were assessed with Fisher's exact test. Other numerical data were assessed by means of one- or two-way analysis of variance, modified for repeated measures, using the SuperANOVA™ software applications (Abacus Concepts, Berkeley, CA, USA) for the Macintosh™ computer (Apple Computer, Cupertino, CA, USA). When inter- and/or intra-group differences occurred, they were further analysed with contrasts. $P<0.05$ was considered significant.

Results

Main procedure

Averaged body weight was 375 (28) g with no significant inter-group differences. Rats given endotoxin twice accounted for 33% (four of twelve rats) of the control group, 50% (four of eight) of the AS-30 group, 27% (three of eight) of the AS-60 group, and 27% (three of eight) of the AS-120 group. The administered dose of endotoxin was 55 (20) mg kg^{-1} with no significant differences among the four groups (Table 1). Elapsed time between the first injection of endotoxin and the starting point for all rats was 184 (81) min with no significant inter-group differences. In all rats arterial pressure decreased after injection of endotoxin. A total of 12 rats died by 180 min after the starting point, and mortality rate of the four groups ranged between 25 and 42% with no significant inter-group differences (Table 1). All rats that died in the control and AS-30 groups suffered from both hypoxaemia and hypotension. In the AS-60 group, one rat died of both hypoxaemia and hypotension, and one hypotension only. In contrast, two rats in the AS-120 group died of hypotension, although Pa_{O_2} was maintained above 27 kPa.

Pa_{O_2} of all rats was 66.0 (8.1) kPa during the baseline period, and decreased to 11.3 (3.3) kPa in the pre-starting period without significant inter-group differences. Changes in Pa_{O_2} are shown in Figure 1A. The reduced Pa_{O_2} of the control group remained less than 12 kPa throughout the observation period (180 min after the starting point). Thirty

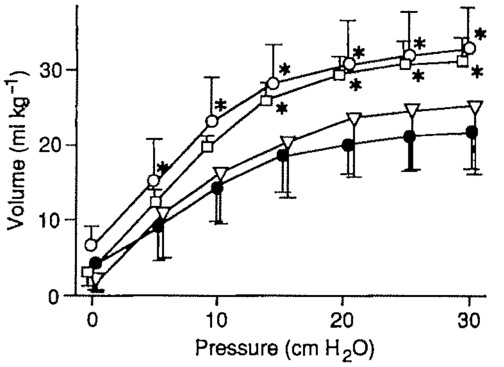

Fig 2 Deflation limbs of static pressure-volume recordings of rat lungs injected with endotoxin. The AS-30 (open triangles, n=8), AS-60 (open boxes, n=8) and AS-120 (open circles, n=8) groups underwent inhalation of an aerosolized MNS for, respectively, 30, 60, and 120 min. The control group (closed circles, n=12) did not receive surfactant. Values show means (SD). * P<0.05 *vs* the control group.

minutes after the starting point, the Pa_{O_2} of the AS-30, AS-60, and AS-120 groups had increased to 33.6 (16.0) kPa (P<0.05 *vs* control group). The Pa_{O_2} of the AS-30 and AS-60 groups, however, gradually decreased after the end of inhalation, and the values at 180 min after the starting point were not significantly different from that of the control group. In contrast, the value for the AS-120 group had increased to 46.1 (12.5) kPa at 120 min, and 52.1 (12.5) kPa 180 min after the starting point (P<0.05 *vs* control group).

Pa_{CO_2} of all rats was 3.5 (0.7) kPa during the baseline period, but increased to 7.3 (2.4) kPa in the pre-starting period with no significant inter-group differences. Changes of Pa_{CO_2} are shown in Figure 1A. The Pa_{CO_2} in the control group remained at approximately 7.3 kPa until the end of the experiment, and that in the AS-30 and AS-60 groups at approximately 6.7 kPa (N.S. *vs* control group). In contrast, the Pa_{CO_2} in the AS-120 group decreased gradually, reaching 5.3 kPa at 120 min after the starting point (P<0.05 *vs* control group).

Deflation limbs of the static pressure-volume recordings of the lung are shown in Fig. 2. Volumes of the AS-30 group did not differ significantly from those of the control group at any pressure. The volumes of the AS-60 group were significantly greater than those of the control group at airway pressures from 30 (maximal pressure) to 15 cm H_2O, while significant differences between the AS-120 and the control groups were observed at airway pressures from 30 to 5 cm H_2O.

Additional procedure

No peroxidase reactions were found in any lung sections stained without anti-SP-B antibody. A typical lung section of a rat with lung-lavage only stained with anti-SP-B is shown in Figure 3A, and that of one with lung-lavage plus inhalation of aerosolized MNS in Figure 3B. The presence of SP-B was seen in the form of brown granules resulting from peroxidase reaction. In the rat with lung-lavage only (Fig. 3A), brown granules were localized almost exclusively within some alveolar epithelial cells mainly at the alveolar corners. Little staining was found along the alveolar wall or terminal bronchioles, thus indicating effective depletion of endogenous surfactant. In the rat with lung-lavage plus inhalation of aerosolized MNS (Fig. 3B), brown granules were found in some parts of the alveolar wall and terminal bronchioles, as well as in some alveolar epithelial cells, indicating deposition of aerosolized MNS onto the alveolar wall and in the terminal airways.

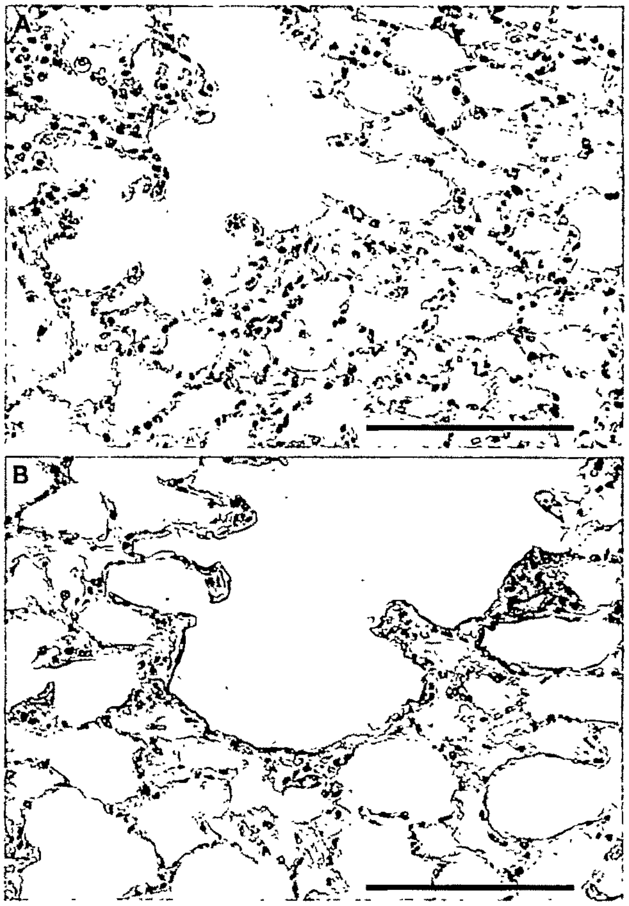

Fig 3 Typical lung sections of a rat with (A) lung-lavage only and (B) of one with lung-lavage plus inhalation of aerosolized MNS. All sections were first counterstained with Meyer's haematoxylin. Presence of SP-B was detected immunohistochemically using anti-SP-B antibody (8B5E antibody),[18] and was seen as brown granules resulting from peroxidase reaction. Magnification of the objective lens was ×20. Bars indicate 100 μm. (A) Brown granules were localized within some alveolar epithelial cells. Very little staining was found along the alveolar wall or terminal airways. (B) Parts of the alveolar wall and terminal bronchioles, as well as some alveolar epithelial cells, were stained with peroxide.

Discussion

In a randomized controlled clinical trial, it was reported that instillation of a MNS, Survanta, administered at 100 mg kg^{-1} up to four times, improved short-term gas exchange and tended to improve survival rates in patients with

ARDS.[8] The results of this trial seem to suggest that multiple administration at large doses of surfactant containing hydrophobic SPs is important. Bolus instillation of surfactant, however, caused a transient but significant decrease in arterial pressure in our previous study.[10] Patients with ARDS or those at risk often manifest circulatory instability, so that bolus instillation may be difficult.

It was reported that slow continuous instillation of surfactant into the airway did not change arterial pressure in lung-lavaged rabbits.[9] However, arterial blood gases were not improved because of inhomogeneous distribution of surfactant in the lung. We have shown that inhalation of aerosolized MNS improves blood gas exchange and lung mechanics without changing arterial pressure in rats with experimental ARDS caused by endotoxin.[10] A recent study using a model of isolated perfused rabbit lung[19] demonstrated that aerosolized surfactant improved ventilation/perfusion mismatch caused by inhalation of a detergent, Tween 20, and that a slow instillation of surfactant did not. The inhalation method, therefore, is superior to slow instillation.

Oxygenation index ($Pa_{O_2}\,FI_{O_2}{}^{-1}$) value for the criteria of ARDS is below 27 kPa and that of acute lung injury is below 40 kPa.[14] In the present study, the oxygenation index of all the rats decreased to well below the criteria of ARDS (11.3 kPa) at the pre-starting point, as the result of the injection of the endotoxin. Inhalation of aerosolized MNS for 30 or 60 min initially restored gas exchange, but Pa_{O_2} deteriorated after termination of the inhalation. In contrast, inhalation for 120 min caused an increase in Pa_{O_2} to 46 kPa at the end of inhalation, and this increase continued after the end of the inhalation period. Inhalation for 120 min also improved Pa_{CO_2} and static lung volume more than that for 30 or 60 min.

It is remarkable that the final Pa_{O_2} value in AS-120 group was as high as the peak value for rats given 100 mg kg^{-1} by instillation of MNS into the airway in our previous study.[10] In that study, intact rats were subjected to inhalation of MNS mixed with $^{99m}TcO_4$. Only 4.2% of the total radioactivity was deposited in the lung. Based on this deposition rate, it was estimated that less than 64 mg kg^{-1} of MNS was deposited in the lungs of the AS-120 group rats as 600 mg was used for inhalation. Inhalation of aerosolized MNS was, therefore, more effective than bolus instillation in terms of the actual amount deposited.

In our additional procedure, deposition of the aerosolized MNS was assessed with the aid of anti-SP-B antibody. Location of aerosol deposition depends on the size of the aerosol.[20] The diameter of the aerosolized MNS produced by our nebulizer (3.4 (1.2) μm) is close to the ideal size for alveolar deposition (2–3 μm).[20] In the rats subjected to repeated lung-lavage without inhalation of aerosolized MNS, there was little staining along the airway or alveolar walls, indicating the effective removal of endogenous surfactant. In rats inhaling aerosolized MNS, the terminal airways and some alveolar walls were stained with peroxide, indicating the deposition of exogenous surfactant. A theoretical model for replacement therapy suggests that surfactant instilled into the airway moves to the alveoli when surface tension in the alveoli is elevated.[21] We believe that aerosolized MNS deposited in both of the alveolar walls and the airways participated in reducing the alveolar surface tension in the main experiment.

In the present study, two of eight rats in the AS-120 group died because of hypotension, although Pa_{O_2} values were maintained higher than 27 kPa. There were no significant differences in mortality rates among the four groups. Endotoxin causes hypotension and massive accumulation of ascites in rats, even when injected through the trachea.[11] Treatment of hypotension may be important to assess the effects on mortality rate. It was reported that a modified bovine surfactant inhibited production of superoxide by neutrophils obtained from hamster with neutrophil alveolitis and promoted apoptosis of neutrophils *in vitro*.[22] The effect of surfactant on neutrophils also needs further investigation.

We conclude that inhalation of aerosolized MNS can improve gas exchange and lung mechanics depending on duration of administration in the experimental setting used for this study. Inhalation for 2 h improved gas exchange to the same extent as was attained with bolus instillation. Prolonged inhalation of aerosolized surfactant, therefore, appears to be suitable for ARDS patients especially with circulatory instability.

Acknowledgements

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References

1 Possmayer F. A proposed nomenclature for pulmonary surfactant-associated proteins. *Am Rev Respir Dis* 1988; **138**: 990–8

2 Johansson J, Curstedt T, Robertson B. The proteins of the surfactant system. *Eur Respir J* 1994; **7**: 372–91

3 Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1993; **147**: 218–33

4 Kobayashi T, Nitta K, Ganzuka M, *et al.* Inactivation of exogenous surfactant by pulmonary edema fluid. *Pediatr Res* 1991; **29**: 353–6

5 Nitta K, Kobayashi T. Impairment of surfactant activity and ventilation by proteins in lung edema fluid. *Respir Physiol* 1994; **95**: 43–51

6 Anzueto A, Baughman RP, Guntupalli KK, *et al.* Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996; **334**: 1417–21

7 Walmrath D, Gunther A, Ghofrani HA, *et al.* Bronchoscopic surfactant administration in patients with severe adult respiratory distress syndrome and sepsis. *Am J Respir Crit Care Med* 1996; **154**: 57–62

8 Gregory TJ, Steinberg KP, Spragg R, *et al.* Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; **155**: 1309–15

9 Segerer H, van Gelder W, Angenent FWM, *et al.* Pulmonary distribution and efficacy of exogenous surfactant in lung-lavaged rabbits are influenced by the instillation technique. *Pediatr Res* 1993; **34**: 490–4

10 Tashiro K, Yamada K, Li WZ, Matsumoto Y, Kobayashi T. Aerosolized and instilled surfactant therapies for acute lung injury caused by intratracheal endotoxin in rats. *Crit Care Med* 1996; **24**: 488–94

11 Tashiro K, Li WZ, Yamada K, Matsumoto Y, Kobayashi T. Surfactant replacement reverses respiratory failure induced by intratracheal endotoxin in rats. *Crit Care Med* 1995; **23**: 149–56

12 Kobayashi T, Kataoka H, Murakami S, and Haruki S. A case of idiopathic respiratory distress syndrome treated by newly developed surfactant (Surfactant CK). *J Jap Med Soc Biol Interface* 1981; **12**: 1–6.

13 Robertson B, Curstedt T, Grossmann G, *et al.* Prolonged ventilation of the premature newborn rabbit after treatment with natural or apoprotein-based artificial surfactant. *Eur J Pediatr* 1988; **147**: 168–73

14 Bernard GR, Artigas A, Brigham KL, *et al.* Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. *Intensive Care Med* 1994; **20**: 225–32

15 Li WZ, Chen WM, Kobayashi T. Aerosolized surfactant reverses respiratory failure in lung-lavaged rats. *Acta Anaesthesiol Scand* 1994; **38**: 82–8

16 Enhörning G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Pediatrics* 1972; **50**: 58–66

17 Lachmann B, Robertson B, Vogel J. In vivo lung lavage as an experimental model of the respiratory distress syndrome. *Acta Anaesthesiol Scand* 1980; **24**: 231–6

18 Suzuki Y, Kogishi K, Fujita Y, Kina T, Nishikawa S. A monoclonal antibody to the 15,000 dalton protein associated with porcine pulmonary surfactant. *Exp Lung Res* 1986; **11**: 61–73

19 Schermuly R, Schmehl T, Günther A, *et al.* Ultrasonic nebulization for efficient delivery of surfactant in a model of acute lung injury. Impact on gas exchange. *Am J Respir Crit Care Med* 1997; **156**: 445–53

20 Cushing IE, Miller WF. Nebulization therapy. In: Safer P. ed. *Respiratory Therapy.* Philadelphia: F A Davis, 1965; 169–218

21 Espinosa FF, Kamm RD. Bolus dispersal through the lungs in surfactant replacement therapy. *J Appl Physiol* 1999; **86**: 391–410

22 Suwabe A, Otake K, Yakuwa N, *et al.* Artificial surfactant (Surfactant TA) modulates adherence and superoxide production of neutrophils. *Am J Respir Crit Care Med* 1998; **158**: 1890–9

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REVIEW ARTICLE

Microvessel damage in acute respiratory distress syndrome: the answer may not be NO†

K. Stuart-Smith[1]* and J. Y. Jeremy[2]

[1] *Department of Anaesthesia, Birmingham Heartlands Hospital, Birmingham B9 5SS, UK.*
[2] *Division of Cardiac, Anaesthetic and Radiological Sciences, Bristol Royal Infirmary, Bristol BS2 8HW, UK*
**Corresponding author*

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Acute lung injury and acute respiratory distress syndrome (ARDS) arise from a wide variety of causes, but the common clinical manifestations are refractory hypoxaemia and increased pulmonary vascular resistance.[66] A major pathological feature of acute lung injury and ARDS is damage to the pulmonary vascular endothelium, secondary to the activation and adhesion of platelets, neutrophils and monocytes.[34 45] This may result in loss of endothelium-derived vasodilators, such as nitric oxide and prostacyclin. Loss of these factors may contribute to the widespread and indiscriminate pulmonary vasoconstriction seen in ARDS, detected clinically as an increase in pulmonary vascular resistance. The clinical consequence is hypoxaemia, since blood flow to ventilated alveoli is limited by vasoconstriction and local thrombus formation. As well as inducing vasodilation, nitric oxide inhibits the release of cytokines and prevents the expression of adhesion molecules in endothelial cells, smooth muscle cells, leucocytes and platelets.[16 39] Thus a simple paradigm might be that damage to the pulmonary vascular endothelium enhances basal tone and the tendency towards vasoconstriction, abolishes endothelium-dependent relaxation and promotes adhesion of platelets and leucocytes, leading to inflammation and pulmonary hypertension.

The vascular endothelium is a complex piece of anatomical and biochemical machinery, especially in the lung, where large and small vessels have a completely different embryonic origin.[4] In *in vitro* studies of the pulmonary circulation, much confusion has arisen because of the use of different generations of vessels, which have different functions, i.e. conduit as opposed to resistance arteries. The true seat of pulmonary vascular resistance in large animals is the pulmonary microvasculature (vessels of $\leq$400 µm in diameter),[20] yet the endothelial responses of these small vessels have hardly been studied. In general terms, in the systemic circulation at least, nitric oxide is a feature of large vessels, whereas a different mediator, endothelium-derived hyperpolarizing factor (EDHF), characterizes microvessels.[25] It would not be unreasonable to speculate that a similar situation occurs in the pulmonary circulation. This article reviews the pathophysiology of ARDS and how the various endothelium-derived relaxing factors (EDRFs) may be affected by the condition. It is suggested that, if the pulmonary microcirculation is the principal source of pulmonary vascular resistance, pulmonary hypertension in ARDS may be linked to loss of EDHF activity, not nitric oxide. If so, inhaled nitric oxide may not be the most appropriate therapy.

Pathophysiology of ARDS

ARDS is a severe and aggressive acute inflammation which is characterized by distinct phases (Fig. 1). In the first phase, invading and dividing bacteria activate polymorphonuclear leucocytes (PMNs; neutrophils) whose primary function is to destroy the bacterial cells.[70] This occurs via the respiratory burst, a surge of superoxide release from the PMNs that kills and fragments bacteria which are then phagocytosed. On destruction, bacteria shed the lipopolysaccharides that make up the bacterial cell wall (endotoxins).[2 54 60] Bacterial endotoxins promote further aggressive adhesion of PMNs, monocytes and platelets to the endothelium as well as to each other.[38 39 55] In the bone marrow, endotoxins cause an indiscriminate release of mature and immature PMNs. These newly released PMNs are less deformable than normal leucocytes, and this feature, coupled with reduced transit times through the diseased

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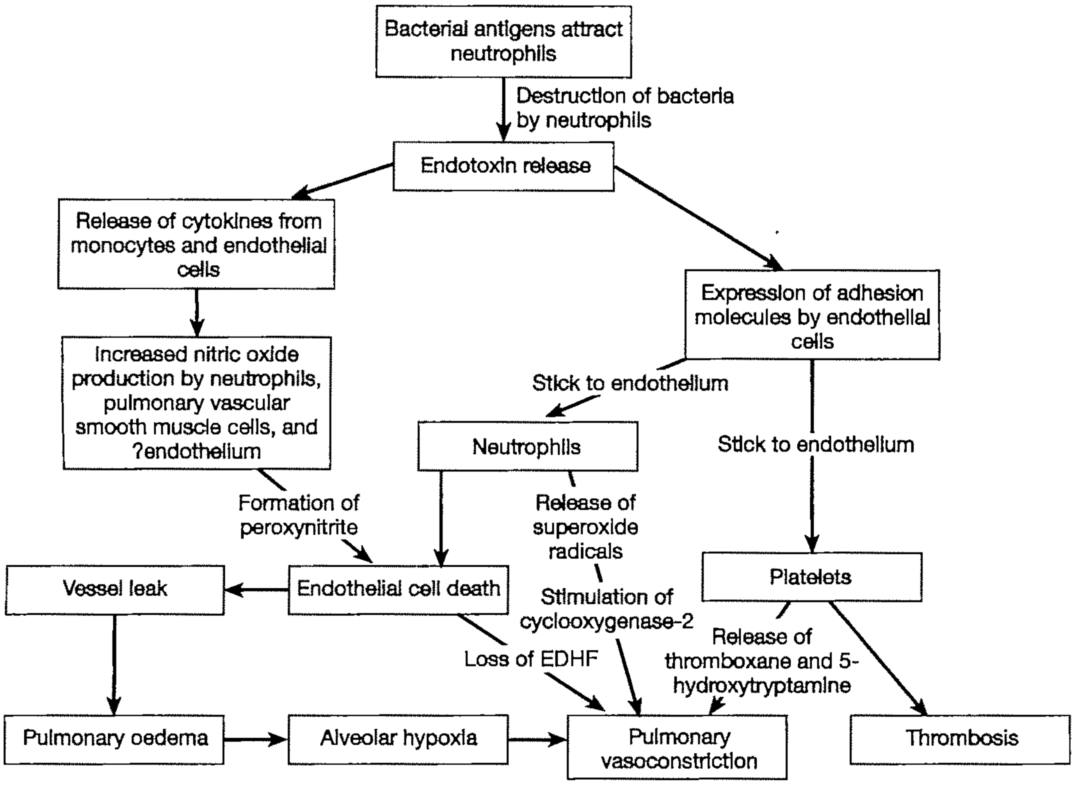
Bacterial antigens attract neutrophils
Destruction of bacteria by neutrophils
Endotoxin release
Release of cytokines from monocytes and endothelial cells
Expression of adhesion molecules by endothelial cells
Increased nitric oxide production by neutrophils, pulmonary vascular smooth muscle cells, and ?endothelium
Stick to endothelium
Neutrophils
Stick to endothelium
Formation of peroxynitrite
Release of superoxide radicals
Vessel leak
Endothelial cell death
Stimulation of cyclooxygenase-2
Platelets
Release of thromboxane and 5-hydroxytryptamine
Loss of EDHF
Pulmonary oedema
Alveolar hypoxia
Pulmonary vasoconstriction
Thrombosis

Fig 1 The inflammatory cascade induced by endotoxin release from bacteria in the pulmonary circulation, and the clinical consequences.

pulmonary circulation, makes PMNs more likely to adhere to the pulmonary microvascular endothelium.

Neutrophils directly damage endothelial cells, in the same way as they damage bacteria, through oxidative bursts.[33 67] Activated leucocytes release cytokines, including tumour necrosis factor alpha (TNFα) and interleukin-1β. These substances stimulate the expression of adhesion molecules in endothelial and vascular smooth muscle cells, thus promoting further adhesion of neutrophils, monocytes and platelets. Proteases, thrombogens and vasoconstrictors are also released.[39]

Several hours after the onset of infection, wide gaps appear in the endothelial cell layer, allowing free passage of PMNs and monocytes to the underlying smooth muscle to promulgate the ongoing cascade. Microvascular fluid leakage results in pulmonary oedema. Since fluid-filled alveoli are not available for gaseous exchange, local hypoxic vasoconstriction occurs, inducing pulmonary hypertension. Hypoxia-induced microvascular constriction reduces flow, further increasing the likelihood of leucocyte adhesion and increasing the likelihood of endothelial damage. In this environment, alteration of the relationship between EDRFs and the underlying vascular smooth muscle is inevitable.

EDRFs and their fate in ARDS

Nitric oxide

The demonstration by Furchgott and Zawadski that endothelial cells could alter the function of vascular smooth muscle introduced a new paradigm in vascular pharmacology.[24] These workers demonstrated that acetylcholine applied to blood vessels with intact endothelium caused vascular smooth muscle to relax. When the endothelium was rubbed off (as was common practice in those days to achieve a 'pure' smooth muscle preparation), acetylcholine caused a small contraction. Over the next few years it was determined by experimental deduction that this EDRF was a diffusible, short-lived highly reactive species which induced relaxation by activating smooth muscle cyclic GMP.[23] By 1986 it was becoming clear that a nitrogen-containing molecule could fit these criteria; the most likely such molecule was a simple, unstable molecule: nitric oxide. Late in 1986, Louis Ignarro's group published evidence suggesting that the pharmacological profiles of nitric oxide and EDRF were identical.[37] Shortly thereafter, the group of Salvador Moncada isolated nitrite products (oxidized forms of nitric oxide) from a blood vessel perfused with acetylcholine. EDRF had been conclusively demonstrated to be nitric oxide.

Nitric oxide is released by a number of dilators, including acetylcholine, bradykinin and substance P.[7] Shear stress is also a potent stimulator of nitric oxide release from endothelial cells.[38 64] All these mediators stimulate release of nitric oxide from the endothelial cell by increasing intracellular concentrations of inositol trisphosphate. This results in the release of Ca^{2+} from intracellular stores in conjunction with calmodulin, to form a calcium–calmodulin complex which activates endothelial nitric oxide synthase.

L-Arginine is converted to L-citrulline, producing nitric oxide.[7 29] Nitric oxide diffuses to the vascular smooth muscle, where it activates guanylyl cyclase and causes an increase in cyclic GMP concentration. Cyclic GMP probably elicits vascular relaxation by causing re-uptake of calcium into the sarcoplasmic reticulum.[29 53]

Nitric oxide as a therapeutic strategy in ARDS

Before the discovery of nitric oxide, the pulmonary hypertension associated with respiratory failure was notoriously difficult to treat, because the available pulmonary vasodilators, such as sodium nitroprusside, prostacyclin, isoprenaline and tolazoline, had to be given intravenously. Although these agents reduced pulmonary arterial pressure, they did so by inducing global pulmonary vasodilation, thereby increasing perfusion to underventilated areas, and so worsening the degree of shunt.[56] In addition, these drugs caused systemic hypotension. Inhaled nitric oxide is delivered to the ventilated alveoli, where it crosses the alveolar membrane to effect vasodilation of the underlying vascular smooth muscle, detected clinically as a reduction in pulmonary vascular resistance.[61] The first evidence for the beneficial effect of inhaled nitric oxide in pulmonary hypertension was published in 1991,[56] and a large volume of literature has been published since, demonstrating that inhaled nitric oxide can reduce pulmonary artery pressures without worsening shunt or inducing systemic hypotension.[63] Consequently, inhaled nitric oxide has been hailed as a major step forward in the treatment of pulmonary hypertension associated with ARDS.

This best clinical response to inhaled nitric oxide is variable and fraught with problems. First, some adult intensive care patients with type 1 respiratory failure do not respond to inhaled nitric oxide therapy: 30–40% of patients with increased pulmonary artery pressure and hypoxaemia do not respond to nitric oxide.[78] Second, the effect of nitric oxide on pulmonary hypertension is transient, being most effective in the first 24 h after onset of symptoms.[50] Third, the effect of nitric oxide is dose dependent, but not in the way that might be expected. Very low dose nitric oxide is beneficial in patients with ARDS, but at high doses of nitric oxide, systemic oxygenation is, paradoxically, worsened, even though pulmonary vascular resistance continues to decrease.[26] All of these factors make the response of individual patients to nitric oxide unpredictable, and may contribute to the observed lack of effect of nitric oxide therapy on outcome in the intensive care unit. To understand how such a situation might come about, it is necessary to examine how nitric oxide affects the pathology of ARDS.

Nitric oxide and the pathology of ARDS

Cytokines enhance the expression of inducible nitric oxide synthase,[17 40] principally from vascular smooth muscle cells (Fig. 1). Cytokine activity also causes both endothelial cells and and neutrophils to increase production of superoxide. Some superoxide production occurs normally in all cells, as a result of metabolic activity. In non-diseased cells, the enzyme superoxide dismutase traps superoxide, preventing mitochondrial damage. In diseased cells, overproduction of superoxide has two consequences. First, the increased volume of superoxide production overwhelms the capacity of superoxide dismutase, even though the amount of this enzyme is increased. Second, and most importantly, superoxide reacts three times more efficiently with nitric oxide than superoxide dismutase.[75] The combination of enhanced nitric oxide production by the vascular smooth muscle cells and superoxide from the endothelial cells results in the formation of the free radical peroxynitrite, a cell poison.[14 27 75]

The introduction of inhaled nitric oxide to this environment has several effects. The first is pulmonary vasodilation in ventilated areas, secondary to the stimulation of vascular smooth muscle cyclic GMP. This is the beneficial effect seen in the first 24 h. Continued administration of nitric oxide will have the following effects: (1) inhaled nitric oxide stimulates lung macrophages to produce superoxide radicals and stimulates inducible nitric oxide synthase in these cells;[73 74] (2) nitric oxide inhibits mitochondrial metabolic activity.[51 75] This further contributes to superoxide formation (by inhibition of the electron transport system).[9] Delivery of a high inspired oxygen concentration to the patient will also result in an increased delivery of superoxide radicals to the lung. Superoxide and nitric oxide from all these sources will interact to form high levels of peroxynitrite, a pulmonary irritant and an irreversible inhibitor of mitochondrial function.[75] Peroxynitrite is found in abundance in the lungs of patients with ARDS.[44] Peroxynitrite (and nitric oxide *at therapeutic concentrations*) destroy surfactant by lipid peroxidation[6] and prevent further surfactant production by mitochondrial poisoning of alveolar type II cells.[31] It may be speculated that this would enhance the tendency to alveolar collapse. Nitric oxide may also exacerbate the alveolar epithelial permeability induced by inflammatory cytokines, an effect most likely mediated by peroxynitrite.[47] Peroxynitrite damages pulmonary arterial endothelium, which will profoundly affect the production of EDRFs.[3] This substance also inhibits the potent pulmonary vasodilator prostacyclin by a direct action, and encourages the formation of the vasoconstrictor, prostaglandin H_2.[79] Peroxynitrite produces a slow relaxation of the pulmonary artery,[15] possibly due to lack of ATP for smooth muscle cell contraction. This may contribute to the initial decrease in pulmonary vascular resistance during the first 24 h of inhaled nitric oxide administration. Tachyphylaxis to peroxynitrite develops and contributes to the general loss of vascular relaxant activity seen in ARDS.[3] Therefore, while nitric oxide initially reduces pulmonary vascular resistance, accumulating toxic metabolites predispose the pulmonary arterial circulation to constriction through the various mechanisms described above. It is proposed that this may be partly responsible for the rebound hypertension seen in a sub-group of patients where inhaled nitric oxide is withdrawn, even when the gas no longer appears to have a therapeutic effect, i.e. nitric oxide may no longer induce active relaxation, but in some patients, may nevertheless protect against vasoconstriction, in spite of its toxic effects. When the nitric oxide is withdrawn, rebound hypertension may occur.

Eicosanoids (products of cyclo-oxygenase)

Prostaglandins, in particular prostacyclin and prostaglandin E_2, are produced by vascular endothelia and elicit vascular smooth muscle relaxation. Like nitric oxide, they also inhibit adhesion of platelets, neutrophils and monocytes and as such prevent thrombus formation and protect against leucocyte-induced damage to the endothelium.[38 39] Inhaled prostacyclin has been used with some success in primary pulmonary hypertension and does improve arterial oxygenation in ARDS, although the effect of this agent on outcome has not been defined. By contrast, other cyclo-oxygenase products have deleterious effects in ARDS. Cytokines promote the expression of cyclo-oxygenase-2 in vascular smooth muscle cells,[1] resulting in increased local formation of thromboxane A2. A study performed in patients after oesophagogastrectomy has shown that those who develop ARDS have significantly greater pulmonary thromboxane production than those without respiratory complications.[65] Both endotoxin and TNFα increase the release of prostaglandin E_2 from pulmonary vascular endothelial cells, particularly in the microvasculature.[49] Although a vasodilator, prostaglandin E_2 is a classic inflammogen in that it promotes capillary leak and thus may contribute to pulmonary oedema in ARDS.[39]

Endothelium-derived hyperpolarizing factor

Even before the discovery of nitric oxide, some workers were able to elicit endothelium-dependent relaxations in various blood vessels which did not fit the accepted view of EDRF.[21] By the mid-to-late 1980s, it was clear that some component of EDRF could hyperpolarize vascular smooth muscle, and the term endothelium-derived hyperpolarizing factor (EDHF) was coined.[12] Although endothelium-dependent hyperpolarization of vascular smooth muscle is elicited by the action of acetylcholine on endothelial cells, it is not affected by known inhibitors of nitric oxide synthase and so cannot involve the L-arginine pathway. It is not a prostaglandin, as inhibition of cyclo-oxygenase enzymes has no effect.[22] While EDHF always causes hyperpolarization, it is not always associated with vascular smooth muscle relaxation.[43] This property has not been explained.

What is EDHF?

In spite of considerable effort, the identity of EDHF remains a mystery. Originally the sequence of events was thought to be diffusion of EDHF from the endothelium to the vascular smooth muscle cell, where opening of potassium channels in the smooth muscle membrane initiated outflow of potassium and hence hyperpolarization of the cell.[22] Whereas the diffusion of nitric oxide was easily demonstrated, diffusion of EDHF from endothelial cell to smooth muscle cell has never been shown convincingly, in spite of some early successes.[57] Close apposition of the two cell types is probably required for transmission of EDHF. This probably explains why EDHF is more prominent in the microvessels, where the endothelial layer is related to a single layer of vascular smooth muscle cells, unlike conduit arteries, which are characterized by multiple smooth muscle layers.[77]

Mechanism of hyperpolarization

Another complex issue is the type of potassium channels involved in the hyperpolarization. Inhibition of endothelium-dependent hyperpolarization by the *combination* of two potassium channel blockers, charybdotoxin and apamin, is the only commonly agreed characteristic of EDHF activity.[19] Charybdotoxin inhibits large conductance calcium-dependent potassium channels, whereas apamin inhibits small conductance calcium-dependent potassium channels. They do not block EDHF when administered separately.[25] This unique property of EDHF has not been explained. Either two separate potassium channels need to be inhibited to block the effect of EDHF, or a single unidentified potassium channel (for example, a voltage-dependent calcium channel) is involved.

This issue is crucial to understanding the role of a particular group of arachidonic acid metabolites, the epoxyeicosatrienoic acids (EETs), in EDHF function. This family is derived by the action of cytochrome P450-dependent enzymes, the epoxygenases, on arachidonic acid, a component of the cell membrane. Epoxygenases are abundant in endothelial cells and show some sequence homology with nitric oxide synthases. When applied topically to vascular smooth muscle cells, EETs cause hyperpolarization and relaxation by opening of smooth muscle potassium channels, so they are candidates for the EDHF response.[10] Unfortunately, direct application of EETs to vascular smooth muscle does not cause relaxation in some vessels where the EDHF phenomenon can clearly be demonstrated.[11] With regard to smooth muscle hyperpolarization, EETs operate large conductance potassium channels exclusively, and so are blocked by charybdotoxin alone.[10] Further, inhibition of epoxygenase enzymes seems to block endothelium-dependent hyperpolarization of smooth muscle cells in some arteries but not others.[13] Overall, the evidence suggests that EDHF cannot be explained simply by secretion of EETs from the endothelium and a subsequent direct action of these substances on the vascular smooth muscle cell.

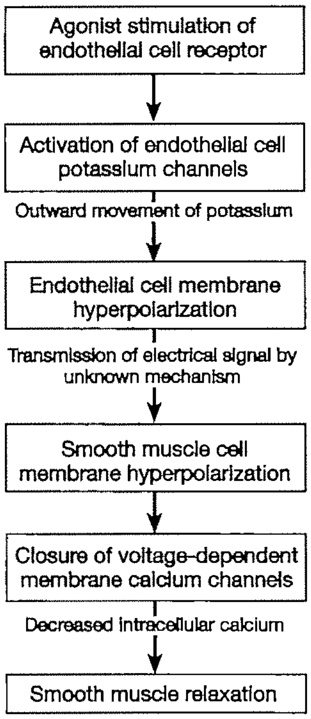
Agonist stimulation of endothelial cell receptor
Activation of endothelial cell potassium channels
Outward movement of potassium
Endothelial cell membrane hyperpolarization
Transmission of electrical signal by unknown mechanism
Smooth muscle cell membrane hyperpolarization
Closure of voltage-dependent membrane calcium channels
Decreased intracellular calcium
Smooth muscle relaxation

Fig 2 Known steps in the sequence of events leading to endothelium-dependent hyperpolarization and relaxation of vascular smooth muscle.

Recently, an alternative and more likely sequence of events has been investigated (Fig. 2). It has been shown that receptor-mediated breakdown of endothelial cell membrane arachidonic acid causes an increase in endothelial EET levels.[28] The EETs stimulate a rise in intracellular calcium, which in turn may be responsible for activation of calcium-sensitive potassium channels on the endothelial cell membrane.[35] These may be the charybdotoxin- and apamin-sensitive potassium channels that are classically associated with the EDHF phenomenon. Elegant electrophysiological experiments by several groups have now shown that these channels are on endothelial cells rather than on vascular smooth muscle cells.[18 58] Thus, receptor-mediated breakdown of endothelial arachidonic acid leads to the intracellular accumulation of EETs, followed by opening of cell membrane potassium channels, outward movement of potassium and hyperpolarization of the endothelial cell. Hyperpolarization of the smooth muscle cell follows. The transmission of EDHF is thus a series of electrical events carrying a signal from the endothelial cell to the smooth muscle cell. This explains the apparent requirement for close apposition of the endothelium to the smooth muscle cell in order to observe the EDHF response.

Transmission of the EDHF signal

How is the signal transmitted across the intracellular space? One prominent group publishing in *Nature* has proposed that, during hyperpolarization of endothelial cells, there is a small net outward movement of potassium ions, which cross the intercellular space to open barium-sensitive potassium channels on the smooth muscle cell, precipitating hyperpolarization of the smooth muscle cell.[18] This group considered that potassium ions could be described as an EDHF. The concentration of potassium ions in the intercellular space is crucial to this argument. If the potassium ion concentration remains below 5 mM, only the potassium channels will be activated and hyperpolarization occurs. Above this level, the direct action of potassium on the cell membrane will initiate depolarization of smooth muscle and so initiate contraction. Therefore, this initially attractive theory has a difficult conceptual problem: the number of potassium ions crossing the intercellular gap and negotiating the basal lamina between the two cell types has to be sufficient to initiate hyperpolarization, but still low enough to avoid depolarization of the smooth muscle cell membrane.[71] Such a fine degree of regulation would be unprecedented. The majority of groups who have subsequently tested this theory have had limited success in reproducing the original findings, although the rat hepatic artery investigated in the *Nature* paper may be a special case.[19 46 58] Generally, it is accepted that while potassium is crucial to the EDHF phenomenon, the exact role of this ion remains undefined.

How, then, is the electrical signal transmitted? Many recent investigations have implicated electrical conduits between the endothelial and smooth muscle cell; so-called myo-endothelial gap junctions.[69 76 77] Gap junctions are formed by a number of membrane proteins, the connexins. Many connexins have been described and are named according to their molecular weight; connexins 37, 40 and 43, for example, are common in blood vessels. Six connexin proteins unite to form a connexon, and several connexons make up a gap junction plaque. Gap junctions are channels linking one cell with another. The channels are large enough to transmit ions and small molecules.[8] The fluid within the junction has an electrical conductance which depends on the connexins present in the channel.[62] Gap junctions are attractive as mediators of vascular smooth muscle function as their connexin composition changes rapidly in response to local changes in shear stress and flow.[68] These areas of close communication are far more common in the thinner-walled microvessels than in large vessels.[48 76] Pharmacological disruption of gap junctions blocks the action of EDHF, suggesting that these structures are conduits for the hyperpolarizing signal. When endothelial cell membrane potential and smooth muscle membrane potential are measured simultaneously in an intact vessel, application of acetylcholine causes both cells to hyperpolarize. After administration of the gap junction inhibitor, 18α-glycyrrhetinic acid, hyperpolarization of endothelial cells still occurs, but not that of smooth muscle, indicating that the EDHF signal has been blocked.[77] These data represent good evidence for a role for gap junctions in EDHF. Unfortunately, as with the EETs, the predominance of the gap junction in EDHF responses varies among different blood vessels. Most authors now believe that both are involved but that the relative importance of EETs and gap junctions is highly variable, making a unifying hypothesis of EDHF action impossible.

EDHF and smooth muscle relaxation

It is simply not clear how EDHF initiates vascular smooth muscle relaxation. Hyperpolarization of the smooth muscle cell membrane by EDHF may close voltage-operated calcium channels, preventing calcium entry (Fig. 2).[5] An alternative and radically different explanation is that stimulation of EETs in the endothelial cells may increase endothelial cyclic AMP concentrations, and that the cyclic AMP may subsequently pass through the gap junction to initiate relaxation.[30] This interesting idea may account for smooth muscle relaxation but not smooth muscle hyperpolarization.

EDHF in the context of the pulmonary microcirculation

Since the pulmonary microvasculature is the source of pulmonary vascular resistance, an understanding of the effects of inflammation on EDHF function is imperative. Such studies are currently in their infancy. Cytokines and lipopolysaccharide increase the production of inducible nitric oxide synthase in pulmonary vascular smooth muscle cells. It has been suggested that the resulting nitric oxide diffuses to the endothelial cells, where it decreases the expression of cytochrome P450 enzymes, reducing EET production and thereby inhibiting EDHF-mediated relaxation.[42]

The effect of inflammation on gap junction activity in the pulmonary circulation is unknown, but there are two highly speculative possibilities. First, alterations in blood flow and shear stress caused by the onset of pulmonary hypertension might lead to a reactive change in myo-endothelial gap junction composition or number,[68] resulting in decreased EDHF activity. Second, gap junctions can be damaged directly by the inflammatory process. Pro-inflammatory mediators specifically disrupt myo-endothelial junctions in the systemic circulation, possibly by altering connexin expression.[36 72] Connexin proteins are manufactured in the endoplasmic reticulum and reach the cell surface after passing through the Golgi apparatus. These manufacturing elements are initially enhanced in pulmonary endothelial cells which are exposed to inflammatory processes, but they are lost as cell injury progresses.[41] Since the turnover rate of connexin proteins in gap junctions is high, loss of cellular manufacturing capacity would inevitably lead to failure of myo-endothelial communication, i.e. loss of EDHF expression.

Conclusion

The discovery of endothelium-derived nitric oxide was only the start of a very complex and exciting story. Vascular smooth muscle function in disease is largely determined by the fate of the endothelium. There are probably many EDRFs, and their character and function are likely to depend on vessel size, location and the effect of environmental factors. In terms of therapy, it initially seemed reasonable to replace lost endothelial factors, as in the use of inhaled nitric oxide and prostacyclin in ARDS. The variable efficacy of these interventions probably reflects the high degree of complexity of the underlying disease process. Inhaled nitric oxide, in combination with high levels of oxygen delivery, may exacerbate the formation of toxic radicals, further damaging the endothelium. The role of a vitally important component, EDHF, has not yet been considered, but its dominant role in the microcirculation means that understanding this complex phenomenon is imperative.

References

1 Akarasereenont P, Bahkle YS, Thiemermann C, Vane JR. Cytokine-mediated induction of cyclo-oxygenase-2 by activation of tyrosine kinase in bovine endothelial cells stimulated by bacterial lipopolysaccharide. *Br J Pharmacol* 1995; **115**: 401–8

2 Bayston K, Cohen J. Bacterial endotoxins. *J Med Microbiol* 1990; **31**: 73–83

3 Benkusky NA, Lewis SJ, Kooy NW. Attenuation of vascular relaxation after development of tachyphylaxis to peroxynitrite *in vivo*. *Am J Physiol* 1998; **275**: H501–8

4 Bohn D. Anomalies of the pulmonary valve and pulmonary circulation. In: Lake CL, ed. *Pediatric Cardiac Anaesthesia*, 3rd Edn. Stamford, Connecticut: Appleton and Lange, 1998; 373–406

5 Bolz S-S, de Wit C, Pohl U. Endothelium-derived hyperpolarising factor but not NO reduces smooth muscle Ca^{2+} during acetylcholine-induced dilation of microvessels. *Br J Pharmacol* 1999; **128**: 124–34

6 Bouhafs RKL, Jarstrand C. Interaction between lung surfactant and nitric oxide production by alveolar macrophages stimulated by group B streptococci. *Ped Pulmon* 2000; **30**: 106–13

7 Bredt DS, Snyder SH. Nitric oxide: a physiologic messenger molecule. *Annu Rev Biochem* 1995; **63**: 175–95

8 Brink PR. Gap junctions in vascular smooth muscle. *Acta Physiol Scand* 1998; **164**: 349–56

9 Brown GC. Nitric oxide inhibition of cytochrome oxidase and mitochondrial respiration: implications for inflammatory, neurodegenerative and ischaemic pathologies. *Mol Cell Biochem* 1997; **174**: 189–92

10 Campbell WB, Gebremedhin D, Pratt PF, Harder DR. Identification of epoxyeicosatrienoic acids as endothelium-derived hyperpolarising factors. *Circ Res* 1996; **78**: 415–23

11 Chataigneau T, Feletou M, Duhault J, Vanhoute, PM. Epoxyeicosatrienoic acids, potassium channel blockers and endothelium-dependent hyperpolarisation in the guinea-pig carotid artery. *Br J Pharmacol* 1998; **123**: 574–80

12 Chen G, Suzuki H, Weston AH. Acetylcholine releases endothelium-derived hyperpolarising factor and EDRF from rat blood vessels. *Br J Pharmacol* 1988; **95**: 1165–74

13 Corriu C, Feletou, M, Canet E, Vanhoutte PM. Inhibitors of the

cytochrome P450-monooxygenase and endothelium-dependent hyperpolarisations in the guinea-pig isolated carotid artery. *Br J Pharmacol* 1997; **117**: 607–10

14 Darley-Usmar V, White R. Disruption of vascular signalling by the reaction of nitric oxide with superoxide: implications for cardiovascular disease. *Exp Physiol* 1997; **82**: 305–16

15 Davidson CA, Kaminski PM, Wolin MS. NO elicits prolonged relaxation of bovine pulmonary arteries via endogenous peroxynitrite generation. *Am J Physiol* 1997; **273**: L437–44

16 De Caterina R, Libby P, Peng HB, Thannicka VJ. Nitric oxide decreases cytokine induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and pro-inflammatory cytokines. *J Clin Invest* 1995; **96**: 60–8

17 Durante W, Schini VB, Kroll MH *et al.* Platelets inhibit the induction of nitric oxide synthesis by interleukin-1β in vascular smooth muscle cells. *Blood* 1994; **83**: 1831–8

18 Edwards G, Dora KA, Gardener MJ, Garland CJ, Weston AH. K$^+$ is an endothelium-derived hyperpolarising factor in rat arteries. *Nature* 1998; **396**: 269–72

19 Edwards G, Gardener MJ, Feletou M, Brady G, Vanhoutte PM, Weston AH. Further investigation of endothelium-derived hyperpolarising factor (EDHF) in rat hepatic artery studies using 1-EBIO and ouabain. *Br J Pharmacol* 1999; **128**: 1064–70

20 Ehrhart IC, Hofman WF. Segmental vascular pressures in lung embolism. *J Appl Physiol* 1993; **74**: 2502–8

21 Feletou M, Vanhoutte PM. Endothelium-derived relaxing factor(s) hyperpolartze(s) coronary smooth muscle. *Physiologist* 1985; **48**: 325

22 Feletou M, Vanhoutte PM. Endothelium-derived hyperpolarising factor. *Clin Exp Pharmacol Physiol* 1996; **23**: 1082–90

23 Furchgott RF. The 1989 von Euler Lecture. Studies on endothelium-dependent vasodilation and the endothelium-derived relaxing factor. *Acta Physiol Scand* 1990; **139**: 257–70

24 Furchgott RF, Zawadzki JV. The obligatory role of the endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373–6

25 Garland CJ, Plane F. Relative importance of endothelium-derived hyperpolarising factor for the relaxation of vascular smooth muscle in different arterial beds. In: Vanhoutte PM, ed. *Endothelium-derived Hyperpolarising Factor.* Amsterdam: Harwood Academic Publishers, 1996; 173–9

26 Gerlach H, Keh D, Falke J. Inhaled nitric oxide: clinical experience. In: Marini JJ, Evans TW, eds. *Update in Intensive Care and Emergency Medicine. 30: Acute Lung Injury.* Berlin: Springer-Verlag, 1999; 353–69

27 Gow AJ, Stephen RT, Ischiropoulos H. Nitric oxide and peroxynitrite-mediated cell death. *Am J Physiol* 1998; **274**: L112–18

28 Graier WF, Simecek S, Sturek M. Cytochrome P450 mono-oxygenase-regulated signaling of endothelial Ca^{2+} entry. *J Physiol* 1995; **482**: 259–74

29 Griffith OW, Steuhr DJ. Nitric oxide synthases: properties and catalytic mechanism. *Annu Rev Physiol* 1995; **57**: 707–36

30 Griffith TM, Taylor HJ. Cyclic AMP mediates EDHF-type relaxations of rabbit jugular vein. *Biochem Biophys Res Commun* 1999; **263**: 52–7

31 Haddad IY, Zhu S, Crow J, Barefield E, Gadhile T, Matalon S. Inhibition of alveolar type II cell ATP and surfactant synthesis by nitric oxide. *Am J Physiol* 1996; **270**: L898–906

33 Harlan JM. Leukocyte–endothelial interactions. *Blood* 1985; **55**: 413–30

34 Hickey MJ, Kubes P. Role of nitric oxide in regulation of leukocyte–endothelial cell interactions. *Exp Physiol* 1997; **82**: 339–48

35 Hoebel BG, Kostner GM, Graier WF. Activation of microsomal cytochrome P450 mono-oxygenase by Ca^{2+} store depletion and its contribution to Ca^{2+} entry in porcine aortic endothelial cells. *Br J Pharmacol* 1997; **121**: 1579–88

36 Hu J, Cotgreave IA. Differential regulation of gap junctions by pro-inflammatory mediators *in vitro*. *J Clin Invest* 1997; **99**: 2312–16

37 Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci USA* 1987; **84**: 9265–9

38 Jeremy JY, Nystrom ML, Barradas MA, Mikhailidis DP. Eicosanoids and septicaemia. *Prostagl Leukotr Essential Fatty Acids* 1994; **50**: 287–97

39 Jeremy JY, Mehta D, Bryan AJ, Lewis D, Angelini GD. Platelets and saphenous vein graft failure following coronary artery bypass surgery. *Platelets* 1997; **8**: 295–309

40 Joly GA, Schini VB, Vanhoutte PM. Balloon injury and interleukin-1β induce nitric oxide synthase activity in rat carotid arteries. *Circ Res* 1992; **71**: 331–8

41 Jones R, Kirton OC. Lung microvessel injury from peritoneal abcesses and gram-negative bacteremia. *Microvasc Res* 1996; **52**: 84–100

42 Kessler P, Popp R, Busse R, Schini-Kerth VB. Pro-inflammatory mediators chronically down-regulate the formation of the endothelium-derived hyperpolarising factor in arteries via a nitric oxide/cyclic GMP-dependent mechanism. *Circulation* 1999; **99**: 1878–84

43 Komori K, Lorenz RR, Vanhoutte PM. Nitric oxide, ACh, and electrical and mechanical properties of canine arterial smooth muscle. *Am J Physiol* 1988; **255**: H207–12

44 Kooy NW, Royall JA, Ye YZ, Kelley R, Beckman JS. Evidence for *in vivo* peroxynitrite production in human acute lung injury. *Am Rev Respir Dis* 1995; **151**: 1250–4

45 Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci USA* 1991; **88**: 4651–5

46 Lacy PS, Pilkington G, Hanvesakul R, Fish HJ, Boyle JP, Thurston H. Evidence against potassium as an endothelium-derived hyperpolarising factor in rat mesenteric small arteries. *Br J Pharmacol* 2000; **129**: 605–11

47 Li XY, Donaldson K, MacNee W. Lipopolysaccharide-induced alveolar epithelial permeability. The role of nitric oxide. *Am J Respir Crit Care Med* 1998; **157**: 1027–33

48 Little TL, Xia J, Duling BR. Dye tracers define differential endothelial and smooth muscle coupling patterns within the arteriolar wall. *Circ Res* 1995; **76**: 49

49 Meyrick B, Christman B, Jesmok G. Effects of recombinant tumour necrosis factor-α on cultured pulmonary artery and lung microvascular endothelial monolayers. *Am J Pathol* 1991; **138**: 93–101

50 Michael JR, Barton RG, Saffle JR *et al.* Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. *Am J Respir Crit Care Med* 1998; **157**: 1372–80

51 Moncada S. Nitric oxide and cell respiration: physiology and pathology. *Verh K Acad Geneeskd Belg* 2000; **62**: 171–9

52 Moncada S, Radomski MW, Palmer RMJ. Endothelium-derived relaxing factor: identification as nitric oxide and role in the control of vascular tone and platelet function. *Biochem Pharmacol* 1988; **37**: 2495–501

53 Nathan C, Xie QW. Regulation of biosynthesis of nitric oxide. *J Biol Chem* 1994; **269**: 13725–8

54 Niu X-F, Smith CW, Kubes P. Intracellular oxidative stress induced by nitric oxide synthesis inhibition increases endothelial cell adhesion to neutrophils. *Circ Res* 1994; **74**: 1133–40

55 Nystrom M, Barradas MA, Jeremy JY, Mikhailidis DP. Effect of endotoxins on platelet shape change. *Thrombosis Haemostasis* 1994; **71**: 646–50

56 Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. *Lancet* 1991; **338**: 1173–4

57 Popp R, Bauersachs J, Hecker M, Fleming I, Busse R. A transferable, β-naphthoflavone-inducible hyperpolarising factor is synthesised by native and cultured porcine artery endothelial cells. *J Physiol* 1996; **497**: 699–709

58 Quignard J, Feletou M, Thollon C, Vilaine J, Duhault J, Vanhoutte PM. Potassium ions and endothelium-derived hyperpolarising factor in guinea-pig and porcine coronary arteries. *Br J Pharmacol* 1999; **127**: 27–34

59 Quignard J, Feletou M, Edwards G, Duhault J, Weston AH, Vanhoutte PM. Role of endothelial cell hyperpolarisation in EDHF-mediated responses in the guinea-pig carotid artery. *Br J Pharmacol* 2000; **129**: 1103–12

60 Radermacher P, Santak B, Becker H, Falke KJ. Prostaglandin E1 and nitroglycerin reduce pulmonary artery capillary pressure but worsen ventilation–perfusion distributions in patients with adult respiratory distress syndrome. *Anaesthesiology* 1989; **70**: 601–6

61 Raetz CR. Biochemistry of endotoxins. *Annu Rev Biochem* 1990; **59**: 130–60

62 Revilla A, Castro C, Barrio LC. Molecular dissection of transjunctional voltage dependence in the connexin-32 and connexin-43 junctions. *Biophys J* 1999; **77**: 1374–83

63 Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide in adult respiratory distress syndrome. *New Engl J Med* 1993; **328**: 399–405

64 Rubanyi GM, Romero JC, Vanhoutte PM. Flow-induced release of endothelium-derived relaxing factor. *Am J Physiol* 1986; **250**: H1145–9

65 Schilling MK, Gassman N, Sigurdsson GH *et al.* Role of thromboxane and leukotriene B4 in patients with acute respiratory distress syndrome after oesophagectomy. *Br J Anaesth* 1998; **80**: 36–40

66 Singh S, Evans TW. The pulmonary circulation in acute lung injury. In: Marini JJ, Evans TW, eds. *Update in Intensive Care and Emergency Medicine. 30: Acute Lung Injury.* Berlin: Springer-Verlag, 1999; 129–46

67 Smedley LA, Tonnesen MG, Sandhaus RA. Neutrophil-mediated injury to endothelial cells: enhancement by endotoxin and essential role of neutrophil elastase. *J Clin Invest* 1986; **77**: 1233–40

68 Spray DC. Gap junction proteins. Where they live and how they die. *Circ Res* 1998; **83**: 679–81

69 Taylor HJ, Chaytor AT, Evans WH, Griffith TM. Inhibition of the gap junctional component of endothelium-dependent relaxations in rabbit iliac artery by 18α-glycyrrhetinic acid. *Br J Pharmacol* 1998; **125**: 1–3

70 Van Eeden SF, Kitagawa Y, Klut ME, Lawrence E, Hogg JC. Polymorphonuclear leukocytes released from the bone marrow preferentially sequester in lung microvessels. *Microcirculation* 1997; **4**: 369–80

71 Vanhoutte PM. Old-timer makes a comeback. *Nature* 1998; **396**: 213–15

72 Van Rijen HVM, van Kempen MJA, Postma S, Jongsma HJ. Tumour necrosis factor α alters the expression of connexin 43, connexin 40 and connexin 37 in human umbilical vein endothelial cells. *Cytokine* 1998; **10**: 258–64

73 Weinberger B, Fakhrzadeh L, Heck DE, Laskin JD, Gardner CR, Laskin DL. Inhaled nitric oxide primes lung macrophages to produce reactive oxygen and nitrogen intermediates. *Am J Respir Crit Care Med* 1998; **158**: 931–8

74 Weinberger B, Heck DE, Laskin DL, Laskin JD. Nitric oxide in the lung: therapeutic and cellular mechanisms of action. *Pharmacol Ther* 1999; **84**: 401–11

75 Wolin MS, Davidson CA, Kaminski PM, Favngersh RP, Mohazzab-H KM. Oxidant-nitric oxide signalling mechanisms in vascular tissue. *Biochemistry (Moscow)* 1998; **63**: 810–16

76 Yamamoto Y, Fukuta H, Nakahira Y, Suzuki H. Blockade by 18α-glycyrrhetinic acid of intercellular coupling in guinea-pig arterioles. *J Physiol* 1998; **511**: 501–8

77 Yamamoto Y, Imaeda K, Suzuki H. Endothelium-dependent hyperpolarisation and intercellular coupling in guinea-pig arterioles. *J Physiol* 1999; **514**: 505–17

78 Young JD. Inhaled nitric oxide in acute respiratory failure. *Br J Anaesth* 1997; **79**: 695–6

79 Zou M, Jendral M, Ullrich V. Prostaglandin endoperoxide-dependent vasospasm in bovine coronary arteries after nitration of prostacyclin synthase. *Br J Pharmacol* 1999; **126**: 1283–92

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SHORT COMMUNICATIONS

Influence of sepsis on minimum alveolar concentration of desflurane in a porcine model

B. Allaouchiche[1]*, F. Duflo[1], R. Debon[1], J.-P. Tournadre[1] and D. Chassard[2]

[1]Department of Anaesthesiology and Intensive Care, Hotel Dieu Hospital, Lyon, France. [2]Department of Anaesthesiology and Intensive Care, Hotel Dieu Hospital, Lyon and Department of Research EA 18/96, Claude Bernard University, Lyon, France

**Corresponding author*

The effect of sepsis on the minimum alveolar concentration of desflurane ($\mathrm{MAC}_{\mathrm{DES}}$) in humans and other animals has not been reported previously. The aim of this study was to test the hypothesis that sepsis might alter $\mathrm{MAC}_{\mathrm{DES}}$ in a normotensive septic porcine model. Twenty-four young healthy pigs were premedicated with ketamine 10 mg kg^{-1} i.m and then anaesthesia was established with propofol 3 mg kg^{-1} and the trachea was intubated. Baseline $\mathrm{MAC}_{\mathrm{DES}}$ in each pig was evaluated by pinching with a haemostat applied for 1 min to a rear dewclaw. $\mathrm{MAC}_{\mathrm{DES}}$ was determined by changing desflurane concentrations stepwise until purposeful movement appeared. Pigs were randomly assigned to two groups of 12 animals: the saline group received a 1 h i.v. infusion of saline solution while the sepsis group received a 1 h i.v. infusion of live *Pseudomonas aeruginosa*. Epinephrine and hydroxyethylstarch were used to maintain normotensive and normovolaemic haemodynamic status. In both groups, $\mathrm{MAC}_{\mathrm{DES}}$ was evaluated 5 h after infusion. Significant increases in heart rate, cardiac output, mean pulmonary artery pressure and pulmonary vascular resistance occurred in the sepsis group. $\mathrm{MAC}_{\mathrm{DES}}$ was 9.2% (95% confidence interval (CI) 6.8–10.6%) for the saline group and 6.7% (95% CI: 4.7–10.4) for the sepsis group ($P<0.05$). These data indicate that $\mathrm{MAC}_{\mathrm{DES}}$ is significantly decreased in this normotensive hyperkinetic septic porcine model.

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Patients with sepsis syndrome or septic shock may require general anaesthesia for surgical procedures. Ketamine may be clinically usefully because it avoids sudden afterload reduction and is relatively good at preserving sympathetic nervous system activity.[1] The rapid pharmacokinetics of desflurane allow rapid haemodynamic control.[2] As it has few hepato-renal side effects, desflurane could be an interesting alternative to ketamine in septic patients.[3]

As for other volatile anaesthetic agents, several factors affect the minimum alveolar concentration of desflurane ($\mathrm{MAC}_{\mathrm{DES}}$) in pigs, including age, body temperature, additional anaesthetic drugs, acid–base status, concentrations of carbon dioxide and brain electrolytes, type of supramaximal stimulus and haemodynamics.[4–6]

The pharmacokinetics of desflurane have been well characterized in humans and other animals,[2] but no data are currently available on $\mathrm{MAC}_{\mathrm{DES}}$ requirements in septic animals or patients. The aim of this study was to test whether sepsis can change $\mathrm{MAC}_{\mathrm{DES}}$ requirements in an animal model of sepsis.

Methods and results

With approval of our local animal research committee, 24 healthy young pigs (3–4 months old; mean (SD) weight 23 (2.9) kg) were used. Animals were premedicated with ketamine 10 mg kg^{-1} i.m., then general anaesthesia was induced with propofol 3 mg kg^{-1}. The trachea was intubated and mechanical ventilation started (Sa 2; Dräger, Lübeck, Germany). The circuit was assembled as an open, non-rebreathing system. Desflurane was administered as the sole anaesthetic agent via a calibrated vaporizer (Devapor, Dräger) in 100% oxygen as the carrier gas with a fresh

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gas flow of 7.0 litres min^{-1}. Ventilation was adjusted to maintain end-tidal normocapnia. Inspired and expired gas (end-tidal anaesthetic concentrations) were measured using a calibrated infrared gas analyser (PM 8050, Dräger). Hydration was maintained with a 0.9% NaCl solution.

MAC$_{\mathrm{DES}}$ was assessed in each pig as described previously,[5] beginning with a 10% end-tidal concentration of desflurane. A haemostatic clamp was placed on the hind limb and moved cranially and caudally for 1 min. If no purposeful response was obtained, the desflurane expired concentration was decreased by 20%. Fifteen minutes were allowed to achieve equilibration and the stimulus was repeated. The end-tidal desflurane concentration was decreased further, step by step, until there was purposeful movement. The desflurane concentration was then increased by 0.3% steps, and after the equilibration period, the stimulus was repeated. The desflurane concentration midway between that allowing and that preventing movement was taken to be the MAC$_{\mathrm{DES}}$. Once MAC$_{\mathrm{DES}}$ had been determined, haemodynamics, end-tidal carbon dioxide concentration and core temperature were recorded. Arterial blood samples were simultaneously collected for gas analysis and measurement of plasma lactate concentrations. Pigs were randomly allocated to two groups with carefully prepared opaque sealed envelopes. The saline group received a 1 h infusion of saline solution (1 ml kg^{-1}) and the sepsis group a 1 h i.v. infusion of live *Pseudomonas aeruginosa*. In keeping with previous studies,[7] 0.3 ml of bacteria (5×10^8 cfu ml^{-1}) were infused per 20 kg bodyweight per minute. In both groups, haemodynamic status and core temperature were assessed 30, 60, 120, 180, 240 and 300 min after infusion of bacteria or saline. Hydroxyethylstarch and epinephrine were used shortly after the infusion to maintain a pulmonary artery occlusion pressure (PAOP) between 8 and 15 mm Hg and a mean systemic arterial pressure (MAP) between 60 and 70 mm Hg.[7] MAC$_{\mathrm{DES}}$ was assessed again 5 h after the end of the infusion. One physician assessed MAC before and after infusion and was not aware of the nature of the infusion or of haemodynamic status; another physician was enrolled to administer the infusion and to manage potential sepsis.

MAC$_{\mathrm{DES}}$ data are expressed as median (95% confidence intervals) and were compared using the Mann–Whitney test. Haemodynamic data were compared using the Friedman test. No statistically significant differences in MAC$_{\mathrm{DES}}$ were observed between the groups before saline and bacterial infusion: the median (95% confidence interval) MAC$_{\mathrm{DES}}$ before infusion was 9.7% (8.7–10.4%) in the saline group and 9.5% (8.6–10.3%) in the sepsis group (Figure 1). MAC$_{\mathrm{DES}}$ for the saline group was 9.2% (6.8–10.6%) after saline infusion and that for the sepsis group was 6.7% (4.7–10.4%) after bacterial infusion ($P<0.05$) (Figure 1). The mean pulmonary arterial pressure (MPAP) in the sepsis group was significantly (170%) higher 30 min after the end of perfusion, and then decreased gradually to a steady state with persistent pulmonary hypertension for the remainder of the study when compared with the saline group. Pulmonary vascular resistance had increased significantly (by 333%) in the sepsis group 30 min after the end of the bacterial infusion, then declined but remained significantly higher than that in the saline group (+96%). Heart rate increased continuously 1 h after the end of bacterial infusion (+18%) and increased by the end of the study (+23%). Cardiac output had significantly increased in the sepsis group (+23%) 1 h after the end of bacterial infusion and remained elevated until the end of the study (+60%).

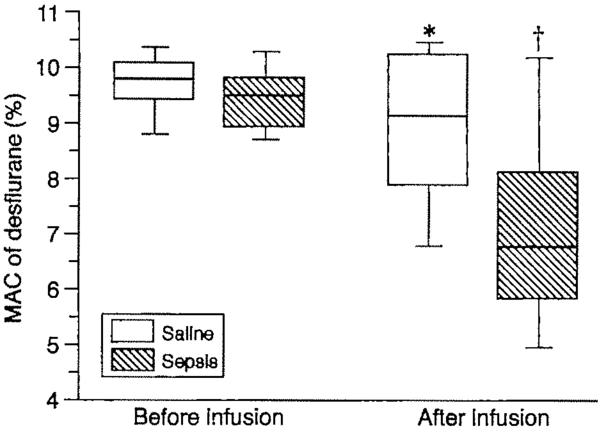

Fig 1 MAC$_{\mathrm{DES}}$ (as a percentage) before (control) and after infusion (saline and sepsis) expressed as median and 95% confidence intervals. *Not significantly different from control after saline infusion. †Significantly different ($P<0.05$) from saline and control after bacterial infusion.

No statistically significant differences in MAP, PAOP, systemic vascular resistance, end-tidal carbon dioxide, arterial gas values, core temperature or plasma lactate concentration were observed. None of the measurements in the saline group after infusion were statistically significantly different from those before infusion.

Comment

Septic animals had a lower MAC$_{\mathrm{DES}}$ than those in the control group. Minimum alveolar concentration has three components: a nociceptive stimulus, a response and an end-tidal anaesthetic concentration.[6] Eger and colleagues defined two types of stimulus for determining MAC in pigs: clamping the dewclaw or clamping the tail.[5] The MAC obtained by clamping the tail was more variable and lower than the that obtained by clamping the dewclaw. The supramaximal stimulus that was applied in our study was dewclaw clamping; purposeful response was said to have been achieved when contralateral movement was obtained.

Many pathophysiological conditions can affect MAC$_{\mathrm{DES}}$, including additional anaesthetic drugs, differences in core temperature, age, acid–base status, concentrations of electrolytes in cerebrospinal fluid, hypotension and prolonged

Table 1 Haemodynamic characteristics of the population. MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PAOP, pulmonary artery occlusion pressure; filling, hydroxyethylstarch infusion. Data are mean (SD). *Significantly different ($P<0.05$) from animals with saline infusion

	Time						
	Before infusion	**30 min**	**60 min**	**120 min**	**180 min**	**240 min**	**300 min**
SVR, dynes s cm^{-5}							
Animals with saline	2261 (119)	1818 (66)	2067 (94)	1878 (63)	1984 (78)	2267 (181)	2397 (194)
Animals with sepsis	2123 (107)	1748 (51)	1659 (56)	1600 (44)	1733 (72)	2012 (126)	1614 (49)
PAOP, mm Hg							
Animals with saline	9 (0.1)	11 (0.3)	10 (0.4)	12 (0.5)	11 (0.2)	10 (0.3)	11 (0.2)
Animals with sepsis	10 (0.3)	9 (0.4)	9 (0.2)	10 (0.3)	12 (0.5)	11 (0.3)	12 (0.4)
MPAP, mm Hg							
Animals with saline	15.4 (1.4)	16.1 (1.2)	17.1 (1.3)	17.5 (1.4)	17.4 (1.4)	16.8 (1.5)	16.4 (1.2)
Animals with sepsis*	19.8 (1)	53 (2.1)	48.2 (1.5)	42.3 (1.5)	39.8 (1.6)	41.8 (1.4)	36.4 (1.1)
PVR, dynes s cm^{-5}							
Animals with saline	269 (38)	287 (35)	297 (42)	275 (31)	302 (39)	304 (43)	285 (38)
Animals with sepsis*	301 (40)	1303 (171)	162 (144)	891 (121)	741 (108)	795 (18)	558 (105)
Heart rate, beats min^{-1}							
Animals with saline	98 (6)	92 (5)	103 (4)	86 (4)	96 (2)	101 (3)	110 (8)
Animals with sepsis*	103 (4)	110 (8)	122 (10)	128 (11)	125 (11)	133 (12)	135 (12)
MAP, mm Hg							
Animals with saline	74 (12)	61 (9)	72 (11)	66 (9)	73 (10)	78 (13)	77 (14)
Animals with sepsis	79 (15)	68 (16)	65 (8)	68 (14)	77 (11)	89 (17)	82 (11)
Cardiac output, litre min^{-1}							
Animals with saline	2.3 (0.2)	2.2 (0.1)	2.4 (0.2)	2.3 (0.1)	2.5 (0.2)	2.4 (0.1)	2.2 (0.1)
Animals with sepsis*	2.6 (0.1)	2.7 (0.2)	2.7 (0.2)	2.9 (0.3	3 (0.2)	3.1 (0.1)	3.5 (0.2)
Core temperature, °C							
Animals with saline	38.2 (0.2)	38.4 (0.3)	38.4 (0.3)	38.4 (0.2)	38.2 (0.2)	38.2 (0.2)	38.3 (0.3)
Animals with sepsis	38.3 (0.2)	38.5 (0.3)	38.5 (0.2)	38.4 (0.3)	38.3 (0.1)	38.3 (0.2)	38.2 (0.1)
Plasma lactate concentration, mmol litre^{-1}							
Animals with saline	0.8 (0.4)						1.1 (0.4)
Animals with sepsis	1.2 (0.6)						1.3 (0.5)
Epinephrine μg kg^{-1} min^{-1}							
Animals with saline	0	0	0	0	0	0	0
Animals with sepsis*	0	0.8 (0.3)	0.6 (0.2)	0.4 (0.1)	0.4 (0.2)	0.3 (0.1)	0.3 (0.1)
Filling, ml							
Animals with saline	0	0	0	0	0	0	0
Animals with sepsis*	0	120 (6)	50 (4)	40 (4)	30 (2)	35 (3)	40 (4)

anaesthesia.[4–6] Premedication with i.m. ketamine and induction with propofol affect MAC_{DES}. Nevertheless, MAC_{DES} values in the two groups were not statistically different before infusion and were close to values reported by Eger and colleagues (10±0.94%).[5] There were no statistically significant differences in core temperature between the groups, so the reduction in MAC_{DES} in the septic group cannot be explained by changes in temperature. Suspected occult tissue hypoxia associated with sepsis could have produced metabolic acidosis, indicating anaerobic metabolism. This phenomenon is likely to have contributed to the decreased anaesthetic requirement.[9] In our study, there was no difference in arterial lactate concentrations or acid–base status. However, lactate is an unreliable indicator of tissue hypoxia in sepsis[10] and, in our septic model, tissue hypoxia could have occurred without metabolic changes. Hypotension has been reported to decrease the MAC of volatile anaesthetic agents.[6] However, in our study, because of epinephrine and hydroxyethylstarch/saline therapy, septic pigs remained normotensive. In the case of haemodynamic failure, MAC_{DES} is likely to be altered more, but this would differ from septic patients undergoing surgical procedures. Another possible explanation of the reduction in MAC_{DES} is cerebral electrolyte dysfunction;[4] in this study we did not measure electrolyte concentrations in cerebrospinal fluid. Another potential cause of discrepancies in the reduction of MAC_{DES} is fluid and drug resuscitation. Hydroxyethylstarch and epinephrine were administered to mimic an anaesthetist's method of sustaining arterial pressure. Steffey and Eger found that epinephrine had no effect on the MAC of halothane in dogs.[11] Our results support the hypothesis that changes in anaesthetic requirement might be related, in part, to the use of hydroxyethylstarch. However, the influence of hydroxyethylstarch on MAC requirements has never been explored. Differences in MAC_{DES} can arise from the central nervous system dysfunction associated with sepsis. Encephalopathy, alterations in neurotransmitter levels, changes in receptor function and brain Ca^{2+} accumulation occur early during sepsis.[1] Changes in regional blood flow and in the energy status of skeletal muscle appear during sepsis.[12] Thus anaesthetic requirements could be reduced in these models and could possibly explain the lower MAC_{DES} in the septic group.

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References

1 Baxter F. Septic shock. *Can J Anaesth* 1997; **44**: 59–72
2 Eger EI II. Desflurane animal and human pharmacology: aspects of kinetics, safety, and MAC. *Anesth Analg* 1992; **75**: S3–9
3 Koblin DD. Characteristics and implications of desflurane metabolism and toxicity. *Anesth Analg* 1992; **75**: S10–6
4 Tanifuji Y, Eger EI II. Brain sodium, potassium, and osmolality: effects on anesthetic requirement. *Anesth Analg* 1978; **57**: 404–10
5 Eger EI II, Johnson BH, Weiskopf RB, *et al.* Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesth Analg* 1988; **67**: 1174–6
6 Quasha AL, Eger EI II, Tinker J. Determination and applications of MAC. *Anesthesiology* 1980; **53**: 315–34
7 Walsh CJ, Surgerman HJ, Mullen PG, *et al.* Monoclonal antibody to tumor necrosis factor α attenuates cardiopulmonary dysfunction in porcine Gram-negative sepsis. *Arch Surg* 1992; **127**: 138–45
8 Eger EI II, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965; **26**: 756–63
9 Gill R, Martin C, McKinnon T, Lam C, Cunningham D, Sibbald WJ. Sepsis reduces isoflurane MAC in a normotensive animal model of sepsis. *Can J Anaesth* 1995; **42**: 631–5
10 James JH, Luchette FA, McCarter FD, Fisher JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet* 1999; **354**: 505–8
11 Steffey EP, Eger EI II. The effect of seven vasopressors on halothane minimum alveolar concentration in dogs. *Br J Anaesth* 1975; **47**: 435–8
12 Illner HP, Shires T. Membrane defect and energy status in rabbit skeletal muscle cells in sepsis and septic shock. *Arch Surg* 1981; **116**: 1302–5

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Loss of volition and pain response during induction of anaesthesia with propofol or sevoflurane

S. Thompson and G. B. Drummond*

Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW, UK
**Corresponding author*

We compared the time to reach two anaesthetic end-points during induction of anaesthesia with a potent inhalation agent (sevoflurane) and an i.v. agent (propofol). We used a method to ensure steady breathing during inhalation induction, and measured loss of tone in the outstretched arm and loss of response to a painful stimulus. Thirty-eight female patients (age 39 (9) yr, weight 65 (11) kg, and height 165 (8) cm) (mean (SD)) were randomly allocated to receive either propofol or sevoflurane. The predicted induction dose of propofol, estimated from age and weight for each patient, was given at a rate of 1% of the induction dose per second, to a possible maximum of 2.5 times the predicted induction dose. Sevoflurane was given with an inhaled concentration of 8%, which was anticipated to cause loss of arm tone within 90–120 s. After loss of consciousness, we applied a painful electrical stimulus to a finger at 15-s intervals and measured the time to loss of motor response. The median times and interquartile values for loss of arm tone were 105 (88–121) s for sevoflurane and 65 (58–80) s for propofol. This was equivalent to 0.65 of the ED_{50} of propofol. The time to loss of response to pain was 226 (169–300) s for sevoflurane. The variances of these three measurements were not significantly different, indicating that these dose–response relationships were similar. In contrast, only 11 of the patients given propofol lost the response to pain after $2.5\times ED_{50}$ had been given. These results support previous evidence of substantial differences between anaesthetic end-points, and show that this evidence can be obtained using a simple and rapid method.

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Clinical investigations of induction of anaesthesia use a variety of measures of anaesthetic effect. Anaesthetics probably do not have a 'single' effect: two obvious separate effects that have been studied are obtunding (loss of volition), and immobilizing (loss of motor response to pain).[1] For some anaesthetics, such as the potent inhalation agents, these effects may be proportional, and have similar dose–response curves. For other types of anaesthetics, such as the i.v. agents, there may be marked differences in the pattern of these effects.

A full examination of the relationship between different measures of anaesthetic action needs stable drug effects obtained in prolonged studies using infusions. If the main interest is the relative distribution of these end-points, for example when comparing agents whose actions are suspected to have different mechanisms, then it is possible to study subjects as the drug effect progressively increases. We have found that the time to loss of lash reflex caused by propofol is more variable than other measures such as loss of voluntary control of breathing and motor activity.[2] We were able to study steadily increasing depth of sevoflurane anaesthesia by using a method which allows breathing to continue without interruption during induction of anaesthesia.[3]

Propofol and sevoflurane are two agents often used to induce anaesthesia for day case surgery. We compared these two different induction agents because they have different patterns of action, comparing a response that is typical of 'obtunding' (loss of position in an arm voluntarily held out) with the classic motor response to a painful stimulus that is used to define anaesthetic potency.

Methods and results

The study was approved by the local ethics committee. We studied patients about to have surgery in the gynaecology day case unit. We asked 49 healthy, English speaking women aged over 16 yr to participate: 43 agreed, and gave written, informed consent. Patients were not recruited if they had received any form of sedation or analgesia in the 12 h before the study. We had no preliminary data that could be used to calculate sample size. We randomized patients by flipping a coin to receive either propofol or sevoflurane in an open, parallel, randomized design. As the rate of administration of i.v. agents affects the apparent potency of the agent,[4] we gave each patient the agent at a rate proportional to the dose appropriate for that patient. We estimated the induction dose of thiopental, using the regression equation of Avram:[5]

$$\text{Dose of thiopental (mg)}=295+\text{weight (kg)} - \text{Age (yr)}\times 1.86$$

The estimated induction dose of propofol was calculated using a potency ratio of 0.53 for propofol.[2] We then took 2.5 times this dose, made up to 50 ml using saline 0.9%, and gave it from a Graseby 3500 syringe driver set to run at 720 ml h^{-1}. In this way, the estimated induction dose should have been given in 100 s. The injection continued until all the end-points had been reached or the whole syringe had been given.

The method of induction with sevoflurane did not require the patient to change her breathing. We added sevoflurane 0.5% to the fresh gas flow, which was oxygen 3 litre min^{-1}. After three breaths, the sevoflurane concentration was doubled to 1%, doubled again after another three breaths, and so on until the maximum concentration of 8% was reached. This level was then maintained until all the end-points had been reached.

The patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Arterial pressure readings were not taken during induction of anaesthesia. During induction, the patient breathed from a co-axial Mapleson D circuit fitted with a side stream carbon dioxide analyser (Datex Cardiocap II). Movements of the reservoir bag and a carbon dioxide trace showing a secondary peak during inspiration indicated rebreathing of the exhaled gas.

Each patient lay supine on a horizontal table. A vein on the dorsum of the left hand was cannulated. Two adhesive silver/silver chloride foil electrodes (Silver Mactrode® Plus, Marquette Medical Systems) were applied, one on each side of the proximal phalanx of the right ring finger, avoiding contact between them. These were connected to the output of a peripheral nerve stimulator (Innervator NS242, Fisher and Paykel). Before breathing from the mask was started, the right arm was held raised and straight, at 45% to the horizontal and away from the side of the patient.

During the induction process, after the patient had closed her eyes and the breathing pattern had changed, we applied a stimulus to the finger (40 mA, 50 Hz, for 2 s), timed to occur every 15 s from the start of anaesthetic administration, until no motor response occurred. A motor response was defined as any movement of the limbs, occurring within 5 s of the stimulus. When all the end-points were reached or after the entire i.v. dose had been given, the study was stopped and anaesthesia continued as appropriate clinically. If the entire dose of propofol was given without all the end-points having occurred, only those end-points that had been reached were analysed.

We used Minitab v.13.1 for statistical analysis. Data were tested for normal distribution using the Anderson–Darling test. The data were displayed visually as cumulative effect against administration time, and are summarized as median and quartiles. The coefficient of variation of the induction times was taken as an index of the slope of the time–response curve. We compared the homogeneity of these coefficients with a method that allows comparison of variances.[6] Significance was set at $P<0.05$.

We plotted a cumulative response–log time curve for each response, using logit values for the proportion of patients that had reached the end-point. These were fitted using weighted linear regression, ignoring values with large standardized residuals. The plot was used to illustrate the

Table 1 Patient details and results. The time to reach each end-point is given. The median time for propofol to abolish response to pain is predicted. The upper quartile value is not given because this end-point was not achieved in nine patients

		Age (yr)	Height (cm)	Weight (kg)		Arm drop (s)	Move (s)
Propofol	Mean	30	165	64	Median	65	230
(n=19)	SD (range)	9 (19–51)	9	9	Quartiles	58–80	129–N/A
Sevoflurane	Mean	29	165	65	Median	105	226
(n=19)	SD (range)	10 (18–45)	8	13	Quartiles	88–121	169–300

relationships and predict the ED_{50} for abolition of movement with propofol.

Of the 43 patients admitted to the study, five were withdrawn for incidental reasons, such as changes in the organization of the operating list. Data from 19 patients in each group who yielded results are presented (Table 1). The two groups were very similar in age, height, and weight. No apnoea, coughing, or excitement occurred in patients induced with sevoflurane.

The end-point of arm descent occurred early during the administration of both agents (Table 1). The median time was less with propofol (65 s) than for sevoflurane (105 s). The abolition of movement by sevoflurane occurred at 226 s, and with more variation (interquartile range, 131 s) compared with the loss of arm tone (interquartile range 33 s). In contrast, eight of the patients who received propofol continued to respond to the electrical stimulus after the entire i.v. dose of $2.5 \times ED_{50}$ had been given. For sevoflurane, the distribution of the times to loss of arm tone and response to a painful stimulus were not significantly different from normal. For propofol a single outlier, with a time of 125 s, made the distribution of values for the loss of arm tone significantly different from normal (P=0.036). Without this value, the distribution did not differ from normal. The variances of the propofol and sevoflurane times for loss of tone were not significantly different (Fig. 1).

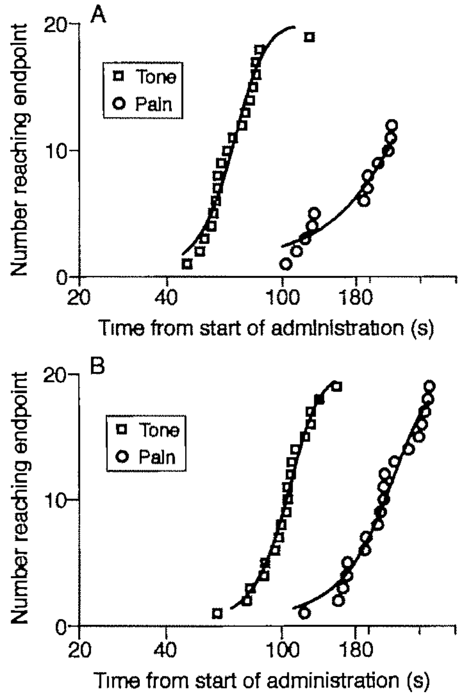

Fig 1 Cumulative numbers of patients achieving the end-points, in relation to time after starting administration of the agent. (A), propofol, (B) sevoflurane. Square symbols, loss of arm tone; circles, loss of response to painful stimulus. The solid lines were fitted using weighted logit linear regression.

Comment

The median time to arm descent was less with propofol than for sevoflurane. Propofol abolished arm tone more rapidly than we had expected. We had planned to give an estimated ED_{50} in 100 s, so that we could reasonably compare the times for propofol and sevoflurane. The data used to estimate the ED_{50} were based on an end-point of drop of a weight, which occurs before arm drop.[2] Induction time could have been reduced by the combination of a slow injection and dilution. Both of these factors increase the apparent potency.[4]

The onset of the effect of sevoflurane is delayed, because the method we used delayed the breathing of effective concentrations of the agent. After this, in the time taken for this study, the alveolar concentration of sevoflurane is likely to be increasing almost linearly. The small fresh gas flow will also reduce the rate of uptake so that alveolar concentration will increase more slowly and thus more linearly over this limited time. The time constant for brain wash-in will depend on the brain–blood partition coefficient, which is 1.7,[7] and brain sevoflurane concentration will lag behind the blood concentration. The increase in brain concentration is also likely to be approximately linear over the time that these measurements were made. Reliable inhalation induction without apnoea is possible if fresh gas flows are reduced.[3]

Response to pain was not lost in eight of the 19 subjects receiving propofol, so satisfactory estimates of the variance could not be made. The fitted curve was constructed using logit values from the patients who did reach the end-point. This predicted a median time to loss of response of 230 s and the lower quartile of the distribution was 129 s (Fig. 1).

The cumulative effect-log time curves appeared sigmoid and this was confirmed by the logit plots. In studies such as this, other factors affect the drug response as well as the mass administered.[4 8] We compared the coefficient of variation of the responses, because the mean time to achieve the responses differed. There was no significant difference in the variance of the time to cause loss of arm tone between the agents. Our findings for the loss of tone, with propofol and sevoflurane, support a previous study of several measures of loss of consciousness, all of which can be loosely considered to indicate obtunding effects (breathing pattern, voluntary movement, weight drop, and arm tone).[2] We also found that the plots for loss of tone and loss of response to pain for propofol, were dissimilar. This is a well recognized feature of propofol.[9] Many consider volatile anaesthetic agents have similar dose–response curves for actions such as loss of consciousness and loss of motor response to pain, but data to support this belief are limited.[10] The additional information provided by this study, using a continuous process of inhalation induction, is valuable confirmation of the similarity.

Despite the simple method we used, comparison of different end-points for a single drug are valid, because the drug effect was progressively increasing. Inhaled agents should ideally be compared using a variety of clinically relevant end-points and in steady state conditions.[11] However, the simple method we describe can demonstrate dissimilar responses.

References

1 Kissin I. General anesthetic action: An obsolete notion? *Anesth Analg* 1993; **76**: 215–8

2 Strickland TL, Drummond GB. Comparison of pattern of breathing with other measures of induction of anaesthesia, using propofol, methohexital, and sevoflurane. *Br J Anaesth* 2001; **86**: 1–6

3 Guracha Boru K, Drummond GB. Comparison of breathing methods for inhalation induction of anaesthesia. *Br J Anaesth* 1999; **83**: 650–3

4 Kazama T, Ikeda K, Morita K, *et al.* Investigation of effective anesthesia induction doses using a wide range of infusion rates with undiluted and diluted propofol. *Anesthesiology* 2000; **92**: 1017–28

5 Avram MJ, Sanghvi R, Henthorn TK, *et al.* Determinants of thiopental induction dose requirements. *Anesth Analg* 1993; **76**: 10–7

6 Zar JH. *Biostatistical Analysis*, 3rd edn. London: Prentice Hall International, 1996; **3**: 206–7

7 Yasuda N, Targ AG, Eger EI. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. *Anesth Analg* 1989; **69**: 370–3

8 Ludbrook GL, Upton RN, Grant C, Martinez A. The effect of rate of administration on brain concentrations of propofol in sheep. *Anesth Analg* 1998; **86**: 1301–6

9 Dunnet JM, Prys-Roberts C, Holland DE, Browne BL. Propofol infusion and the suppression of consciousness: dose requirements to induce loss of consciousness and to suppress response to noxious and non-noxious stimuli. *Br J Anaesth* 1994; **72**: 29–34

10 Prys-Roberts C. A philosophy of anaesthesia: some definitions and a working hypothesis. In: Prys-Roberts C, Brown BR Jr, eds. *International Practice of Anaesthesia*. Oxford: Butterworth-Heinemann 1996

11 Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. *Anesthesiology* 1996; **84**: 38–51

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Influence of nitrous oxide on induction of anaesthesia with sevoflurane†1

H. O'Shea, S. Moultrie and G. B. Drummond*

Department of Anaesthetics, Critical Care, and Pain Medicine, Royal Infirmary, Edinburgh EH3 9YW, UK

**Corresponding author*

Nitrous oxide is often used during inhalation induction of anaesthesia with sevoflurane. Although the value of using nitrous oxide during inhalation induction with other volatile anaesthetics has been studied, the popularity of sevoflurane induction and the different characteristics of this agent make a study of the combination of nitrous oxide with this agent of interest. We compared induction times, oxygenation, and excitatory events during inhalation induction of anaesthesia using sevoflurane, with and without nitrous oxide. We studied 64 female patients, randomly allocated to receive inhalation induction of anaesthesia using sevoflurane with or without 50% nitrous oxide in the fresh gas, using a co-axial breathing system (Mapleson

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D) and a fresh gas flow rate of 3–6 litre min^{-1}. Mean time to induction of anaesthesia (fall of an outstretched arm) was 102 s in both groups, but excitation (limb or head movement) was more frequent in those receiving nitrous oxide (10 patients) than in those receiving oxygen only (five patients) ($P<0.05$). Oxygenation was similar in both groups. We conclude that nitrous oxide confers no advantage when anaesthesia is induced with sevoflurane in this way.

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Sevoflurane is a popular agent for inhalation induction of anaesthesia, primarily because of its acceptability by lack of irritation.[1] The speed of onset of anaesthesia is rapid, and although nitrous oxide is often added to the inhaled gases, there is only little evidence that the combination is much better than sevoflurane used alone.[2 3] We carried out a study to investigate the effects of nitrous oxide on speed and quality of inhalation induction, using a method that requires minimal cooperation from the patient.[4]

Methods and results

After ethics committee approval, we recruited 64 ASA I and II patients about to have gynaecological surgery. Each patient gave written informed consent. No premedication was given. When the patient arrived in the anaesthetic room, an i.v. cannula was placed in the hand and monitors attached (ECG, finger pulse oximetry, non-invasive arterial pressure). After baseline readings were taken, no further arterial pressure measurements were taken during the induction to avoid discomfort. The patient lay supine and horizontal, and was asked to keep one arm held straight out, about 30% up from the horizontal, for as long as possible during the induction. Induction time was taken as the time from the first addition of sevoflurane to the carrier gas, to the time the arm fell to the horizontal. Immediately before induction of anaesthesia, patients were allocated by flipping a coin to receive either nitrous oxide or oxygen alone as the carrier gas, and were not told of this allocation.

A disposable Mapleson D co-axial breathing circuit (Bain circuit) was used. Gas for carbon dioxide analysis (Datex Cardiocap 3) was sampled from the gas source side of a filter fitted to the mask. The flow rate was first set at 10 litre min^{-1} of oxygen. A well fitting facemask was applied and the patient was instructed to breathe normally. The reservoir bag and the capnograph were carefully observed to ensure that no leaks were present, and that a secondary peak of carbon dioxide concentration was present during inspiration, indicating partial rebreathing. After the patient had taken three satisfactory breaths, the gas flow was reduced, to either oxygen of 3 or 1.5 litre min^{-1} and nitrous oxide 1.5 litre min^{-1} according to the random allocation. At the same time 0.5% sevoflurane was set on the vapourizer. After each subsequent three breaths, the sevoflurane concentration was doubled until 8% was reached. If coughing occurred, the concentration increase was not applied until breathing was settled for three breaths. After the sevoflurane concentration had been maintained at 8% for 15 s, fresh gas flow was increased to 6 litre min^{-1}. Any excitatory events such as vocalization, or movements of the head, neck, body or limbs, or reduction of the pulse oximeter reading to less than 94%, was noted. We also noted any cessation of breathing movements for more than 10 s, which was considered to be apnoea.

The study stopped when the arm had come down, and anaesthesia was continued as appropriate clinically. Values are expressed as mean (SD) and compared between the groups with Student's *t*-test (induction time) and the chi-squared test (excitation and apnoea) (Minitab v. 13.1). We accepted $P<0.05$ as significant.

Twenty-six patients received nitrous oxide and oxygen, and 36 patients received oxygen only, as carrier gas. The features and the induction characteristics of the groups are shown in Table 1. The two groups were similar in age and weight. Induction times were very similar: 102 (24) s with nitrous oxide/oxygen, and 102 (27) s with oxygen. The 95% confidence limits for a difference in these times are ±13 s.

Excitation was more frequent (10 out of 26) in the group receiving nitrous oxide than in those who received oxygen (five out of 36) ($P<0.05$). Reduction in Sp_{O_2}. values to less than 94% occurred in two patients breathing oxygen and one patient receiving nitrous oxide, and no decreases were seen in association with excitatory side effects. Apnoea for 16 s

Table 1 Features of patients and characteristics of induction in groups receiving and not receiving nitrous oxide

	Oxygen	Nitrous/oxygen
Number	36	26
Age (range) yr	31 (16–59)	28 (16–50)
Weight (range) kg	65 (48–93)	62 (44–90)
Induction time (SD) s	102 (27)	102 (24)
Patients with excitation	5	10
Patients with Sp_{O_2} <94%	2	1
Patients with apnoea	1	0

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occurred in one patient who received sevoflurane in oxygen, without excitation or a decrease in Sp_{O_2}.

Comments

Sevoflurane and nitrous oxide are commonly used together for induction of anaesthesia[5 6] despite few studies to support the use of this combination. Hall and co-workers compared inhalation induction, using a single breath method, using 8% sevoflurane in either oxygen or 67% nitrous oxide. They found no significant difference in time to induction or complications: moderate excitation in six out of 15 subjects receiving oxygen and three out of 16 receiving nitrous oxide.[3] In that study, they used a vital capacity method which requires some co-operation from the patient, whereas we used a method that relies on mild rebreathing to maintain ventilation during the period of loss of consciousness, and only requires the patient to breathe normally.[4]

The time to induction of anaesthesia in our study was greater than in other studies of inhalation induction, which report times of about 1 min[3 6] presumably because we increased the fresh gas vapour concentration gradually, over about 30 s. However the increased time was offset by the small incidence of excitation and apnoea, which was less than reported by others.[3 5 6]

We did not conceal the use of the carrier gas from the anaesthetist giving the anaesthetic. Although studies that involve an observer assessment of quality should be double blind, we limited our assessment to features that we considered unambiguous: pulse oximeter readings, breathing movements, arm position, and any movement of the head or limbs. Different measures are used to define the induction of anaesthesia, but we have found that the measure we used in this study is equivalent to others, such as loss of voluntary finger tapping.[7] Arm position gave an easily visible endpoint without needing intermittent stimulation of the patient as would occur with finger tapping or loss of lash reflex. It can be affected by excitatory side effects, and in two patients, excitatory effects made the endpoint of arm lowering equivocal. Exclusion of these times from analysis did not affect the statistical conclusion. We studied a sufficient number of patients to find a significant difference in minor and generally clinically insignificant excitation during induction, and found that nitrous oxide had no effect on the time for induction of anaesthesia.

In theory, nitrous oxide can speed induction of anaesthesia by adding its effect to that of sevoflurane, and also perhaps by the second gas effect. However, the concentrations used in this study would limit the importance of the latter mechanism. We cannot be certain what the inspired concentration of nitrous oxide would have been. It would have been less than 50% because of the limited fresh gas flow, and would have increased progressively during the induction process, perhaps reaching excitatory concentrations towards the time at which sevoflurane would be affecting consciousness as well. The system would also have contained some residual nitrogen from the patient's lungs. By using nitrous oxide in the carrier gas, the benefits of pre-oxygenation will be reduced or abolished, with no clear benefit on the process of induction.

We conclude that in young unpremedicated patients, nitrous oxide confers no advantage when added to sevoflurane for inhalation induction.

References

1 Doi M, Ikeda K. Airway irritation produced by volatile anaesthetics during brief inhalation: comparison of halothane, enflurane, isoflurane and sevoflurane. *Can J Anaesth* 1993; **40**: 126–6

2 Yurino M, Kimura H. A comparison of vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentrations in nitrous oxide and oxygen. *Anaesthesia* 1995; **50**: 308–11

3 Hall JE, Stewart JIM, Harmer M. Single-breath inhalation induction of sevoflurane anaesthesia with and without nitrous oxide: a feasibility study in adults and comparison with an intravenous bolus of propofol. *Anaesthesia* 1997; **52**: 410–5

4 Guracha Boru K, Drummond GB. Comparison of breathing methods for inhalation induction of anaesthesia. *Br J Anaesth* 1999; **83**: 650–3

5 Thwaites A, Edmends S, Smith I. Inhalational induction with sevoflurane: a double-blind comparison with propofol. *Br J Anaesth* 1997; **78**: 356–65

6 Philip BK, Lombard LL, Roaf ER, Drake AF, Calalang I, Philip JH. Comparison of vital capacity induction with sevoflurane to intravenous induction with propofol for adult ambulatory anesthesia. *Anesth Analg* 1999; **89**: 623–7

7 Strickland TL, Drummond GB Comparison of signs of anaesthesia using propofol, methohexital and sevoflurane. *Br J Anaesth* 1999; **83**: 180P–1P

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Air flow resistance of three heat and moisture exchanging filter designs under wet conditions: implications for patient safety[†][1]

N. J. Morgan-Hughes[1 3]*, G. H. Mills[1 2] and D. Northwood[3]

[1]Department of Anaesthesia and Intensive Care and [2]Sheffield University Department of Anaesthesia, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. [3]Department of Anaesthesia and Intensive Care, Doncaster Royal Infirmary, Armthorpe Road, Doncaster DN2 5LT, UK

**Corresponding author. Present address: Department of Anaesthesia and Intensive Care, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK*

Heat and moisture exchanging filters (HMEFs) can be blocked by secretions. We have studied HMEF performance under wet conditions to see which particular design features predispose to this complication. Dar Hygrobac-S (composite felt filter and cellulose exchanger), Dar Hygroster (composite pleated ceramic membrane and cellulose exchanger) and Pall BB22-15 (pleated ceramic membrane) HMEFs were tested. Saline retention, saline concealment, and changes in air flow resistance when wet were assessed. The cellulose exchanger in the composite Hygrobac-S and Hygroster retained saline, producing a 'tampon' effect, associated with bi-directional air flow resistances in excess of the international standard of a 5 cm H_2O pressure drop at 60 litre min^{-1} air flow. Furthermore, high air flow resistances occurred before free saline was apparent within the transparent filter housing. The pleat only BB22-15 showed a significant increase in expiratory air flow resistance, but only after the presence of saline was apparent. These data imply that composite HMEFs with cellulose exchangers are more likely to block or cause excessive work of breathing as a result of occult accumulation of patient secretions than pleat only HMEFs.

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Keywords: equipment, heat and moisture exchangers; equipment, bacterial filters; complications

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Heat and moisture exchanging filters (HMEFs) are often used in intensive care to maintain airway humidification and prevent breathing apparatus contamination. Most work concerning the safety of HMEFs in this setting has concentrated on the risk of tracheal tube blockage, a complication that is recognized as inversely related to the moisture output of the device concerned.[1] Accumulation of excess condensation or patient secretions within HMEFs may increase work of breathing[2] and cause device blockage.[3] Most manufacturers warn users of this possibility.

We have examined the performance of three HMEFs under wet conditions in an attempt to determine whether any particular design features might predispose to such complications. The test procedure described assumes that the coexistence of the following factors could cause blockage: (1) a device would have to retain secretions, (2) the retained secretions should not be apparent on inspection of the device, and (3) they would increase air flow resistance across the device.

Methods and results

Dar Hygrobac-S, Dar Hygroster, and Pall BB22–15 HMEFs were studied. All have a transparent plastic housing. The Dar Hygrobac-S is of composite design utilizing both an electrically charged felt filter and a separate cellulose heat and moisture retaining element. The Dar Hygroster is of composite design with a pleated ceramic filter and a cellulose based heat and moisture exchanging element. The Pall BB22-15 is a pleat only design using a pleated ceramic membrane, which acts both as a filter and a heat and moisture exchanger.

Retention testing

Increments of 5 ml 0.9% saline were instilled into the patient end of the device, which was gently shaken with the

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Table 1 Volumes (SD) of saline retained and concealed by devices, also expressed as a percentage of the device patient sided dead space

	Dead space (ml)	Retention volume (ml)	Concealment volume (ml)	Retention volume (% dead space)	Concealment volume (% dead space)
Dar Hygrobac-S	33.6 (0.5)	25 (0)	20 (0)	74 (0)	60 (0)
Dar Hygroster	56.6 (1.5)	25 (0)	25 (0)	44 (0)	44 (0)
Pall BB22-15	53.8 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)

Table 2 Effect of incremental saline challenge on mean (SD) pressure drop across devices at 60 litre min^{-1} inspiratory and expiratory air flow. *Inspiratory testing was continued with the addition of further saline until air flow resulted in the ejection of saline from the patient end of the device. **Expiratory testing was continued with the addition of further saline until the resistance presented by the filter exceeded the pressure generating capabilities of the flow generator (30 cm H_2O)

Saline challenge (ml)	Inspiratory pressure drop (cm H_2O) across devices			Expiratory pressure drop (cm H_2O) across devices		
	DAR Hygrobac-S	DAR Hygroster	PALL BB22-15	DAR Hygrobac-S	DAR Hygroster	PALL BB22-15
0	3.3 (0.32)	3.4 (0.23)	2.4 (0.16)	3.3 (0.37)	2.9 (0.21)	2.3 (0.10)
5	3.8 (0.43)	3.5 (0.33)	2.6 (0.20)	3.9 (0.56)	3.1 (0.21)	2.6 (0.16)
10	4.3 (0.61)	3.9 (0.35)	2.9 (0.22)	5.0 (0.99)	3.4 (0.19)	3.0 (0.18)
15	5.7 (1.11)	5.1 (1.27)	3.7 (0.23)	7.2 (0.71)	4.0 (0.41)	4.0 (1.22)
20	10.8 (3.40)	7.2 (1.46)	Ejection*	23.1 (3.63)	5.6 (0.70)	5.8 (1.57)
25	13.6 (2.40)	8.8 (0.43)		>30**	7.8 (0.59)	9.5 (2.16)
30	Ejection*	Ejection*			12.9 (4.69)	>30**
35					>30**	

patient end occluded and then inverted to determine if spillage of saline occurred. Further increments were added in this manner and the maximum volume instilled that did not result in spillage was defined as the 'retention volume'.

Concealment testing

Increments of 5 ml 0.9% saline were instilled into the patient end of the device, which was gently shaken with the patient end occluded and then inspected for the appearance of free saline within the patient side of the device housing. Further increments were added and the maximum volume instilled that did not result in the appearance of free saline was defined as the 'concealment volume'.

Dead space testing

The dead space of the device on the patient side was measured by adding 1 ml saline increments to the patient end of vertically mounted devices up to the point of spillage.

Five devices of each type were used for each of the above test sequences and mean (SD) values calculated. Retention and concealment volumes were expressed as a percentage of the device dead space on the patient side (Table 1).

Resistance to air flow with incremental fluid challenge

The resistance of each device was measured by connecting it to a continuous air flow generated by a non-invasive pressure support ventilator (BiPAP S/T-D30, Respironics) and the pressure drop across the device measured using a certified calibration analyser (RT-200, Allied Healthcare Products). An air flow of 60 litre min^{-1} was used for all pressure drop measurements.

Inspiratory flow resistance was measured by connecting the air flow to the non-patient end of the vertically mounted device (patient end uppermost). After baseline testing the device was removed from the test rig and 5 ml of 0.9% saline instilled into the patient end. The device was gently shaken with the patient end occluded, reinserted into the test rig and the measurement repeated. Testing continued with the addition of further aliquots of saline until the air flow through the device resulted in ejection of saline from the patient end. Expiratory flow resistance was similarly measured but with the air flow connected to the patient end of the device and with testing continuing until the resistance presented by the filter exceeded the pressure generating capabilities of the BiPAP S/T-D30 (30 cm.H_2O). Ten devices of each type were tested for each air flow direction and mean (SD) values calculated (Table 2).

Comment

This study is limited by the use of saline as a test liquid. Some previous work in this area has been undertaken using water.[4] It would be interesting to look at a range of test liquids, but the variable composition of patient secretions opens the choice of any test liquid to criticism.

Blockage is a recognized complication of HMEF usage and most manufacturers warn users of the potential for accumulated secretions to cause occlusion. The cellulose exchanger of the composite HMEFs in this study retained and concealed large volumes of saline (Table 1). This produced a 'tampon' effect associated with bi-directional air flow resistances well in excess of the international standard of a 5 cm H_2O pressure drop across the device at 60 l min^{-1} air flow (Table 2).[5] The 'tampon' effect was most pronounced in the DAR Hygrobac-S, which had the greatest retention volume when expressed as a percentage of the patient sided device dead space (74%). In the clinical setting such secretion accumulation might be detectable if blood stained or purulent but contamination with clear secretions would not be obvious.

The pleat only HMEF showed a significant increase in expiratory air flow resistance (Table 2) but only after the saline was seen (Table 1). If hanging down and collecting secretions, a pleat only HMEF could allow inspiration, but prevent expiration.[6] However, the filter would have to be held in a dependent position for sputum retention to occur and the patient's attendants would have to fail to notice that the filter housing was full of secretions. Our data suggest that secretions would be seen before expiratory air flow resistance increased significantly.

The superior moisture output of composite HMEFs results in a lower incidence of tracheal tube blockage in comparison to pleat only devices.[1] However our data imply that composite designs may have greater potential to block or cause excessive work of breathing from occult accumulation of patient secretions. In the UK, the Medical Devices Agency performs regular evaluations of HMEFs, however, these are performed in accordance with the International Standard for Anaesthetic and Respiratory Equipment test procedure[5] and do not include a liquid challenge. Testing under wet conditions would provide clinicians with useful information when assessing the safety profile of individual devices and in particular would allow comparison between different designs of composite HMEFs with regard to the risk of device blockage.

References

1 Villafane MC, Cinnella G, Lofaso F, *et al.* Gradual reduction of endotracheal tube diameter during mechanical ventilation via different humidification devices. *Anesthesiology* 1995; **85**: 1341–9

2 Johnson PA, Raper RF, Fisher MMcD. The impact of heat and moisture exchanging humidifiers on work of breathing. *Anaesth Intensive Care* 1995; **23**: 697–701

3 Prasad KK, Chen L. Complications related to the use of a heat and moisture exchanger. *Anesthesiology* 1990; **72**: 958

4 Hedley RM, Allt-Graham J. A comparison of the filtration properties of heat and moisture exchangers. *Anaesthesia* 1992; **47**: 414–20

5 International Organisation for Standards. Anaesthetic and Respiratory Equipment—Heat and Moisture Exchangers for Use in Humidifying Respired Gases in Humans. Geneva: International Organisation for Standardisation Technical Committee, 1992, International Standard ISO 9360,2

6 Wilkes AR. Resistance to gas flow in heat and moisture exchangers. *Anaesthesia* 1992; **47**: 1095

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Touch contamination levels during anaesthetic procedures and their relationship to hand hygiene procedures: a clinical audit

A. F. Merry[1] [2]*, T. E. Miller[3], G. Findon[3], C. S. Webster[1] [2] and S. P. W. Neff[1]

[1]Department of Anaesthesia, Green Lane Hospital, Auckland, New Zealand. [2]Section of Anaesthesia, Department of Pharmacology and [3]Department of Medicine, University of Auckland, New Zealand

**Corresponding author*

After different methods of hand preparation, volunteers rolled segments of sterile central venous catheter between their fingertips, and bacterial transfer was evaluated by standardized quantitative culture. The number of bacteria transferred differed between methods ($P<0.001$). Comparisons were made with the control group (no preparation at all; median, third quartile and maximum count=6.5, 24, 55). Bacterial transfer was greatly increased with wet hands (1227, 1932, 3254; $P<0.001$). It was reduced with a new rapid method, based on thorough drying with a combination of 10 s using a cloth towel followed by either 10 or 20 s with a hot-air towel (0, 3, 7 and 0, 4, 30, respectively; $P=0.007$ and 0.004, respectively). When asked to follow their personal routines, 10 consultant anaesthetists used a range of methods. Collectively, these were not significantly better than control (7.5, 15, 55; $P=0.73$), and neither was an air

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towel alone (2.5, 15, 80; P=0.176) nor the hospital's standard procedure (0, 1, 500; P=0.035). If hand preparation is needed, an adequate and validated method should be used, together with thorough hand drying.

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The effects of hand preparation on skin microbial flora have been studied,[1–3] but there are few studies in the context of the practising anaesthetist. The issue is of importance during procedures, such as the insertion of central venous or epidural catheters, when meticulous sterility is needed. However, notwithstanding formal guidelines that specify a thorough surgical scrub and the use of a sterile gown,[4] we have noticed considerable variation in hand preparation by anaesthetists before sterile procedures.

The aim of washing or scrubbing hands is to reduce to a minimum the transfer of bacteria. Transient contaminants, including Gram-negative bacteria acquired during random contact with various fomites, are readily removed by hand washing. However, hands also harbour resident flora (typically Gram-positive) that are less easily eliminated and that may be transferred by touch. Moisture is a key factor determining the level of touch-associated bacterial transfer following hand washing. We proposed a rapid method of hand drying based on the combined use of a cloth or paper towel and a hot-air towel.[1]

We audited methods of hand preparation for the insertion of a central venous catheter, used routinely by 10 consultants in our department, and compared the efficacies of these methods with those of the hospital's standard method, the proposed dual method of hand preparation, and an air towel alone.

Methods and results

Subjects

The regional ethics committee accepted the study as an audit. Members of the Department of Anaesthesia, selected in groups of 10 on the basis of availability, participated voluntarily.

Hand preparation methods evaluated

The study procedure was carried out after each of seven approaches to hand preparation:

(1) 'Pre-test': dry hands, no prior hand washing;
(2) 'Wet': rinsing hands under cold running tap water for 5 s, no drying;
(3) 'Individual': individual hand washing procedure routinely used by participants (specified as consultants in this group);
(4) 'Hospital': Green Lane Hospital's standard hand washing procedure, which specifies taking 3 min (in total) for three scrubs with either povidone iodine or chlorhexidine soap, and then drying hands on a sterile towel;
(5) 'Air-45': wetting hands under cold running tap water for 5 s, followed by shaking off excess water and placing hands under hot-air drier for 45 s;
(6) 'Cloth-air-10': rinsing hands under cold running tap water for 5 s, followed by shaking off of excess water, drying of hands on a cloth towel (non-sterile, reusable pull down variety) and placing hands under hot-air drier for 10 s;
(7) 'Cloth-air-20': as for (6), but with hands under hot-air drier for 20 s.

The first two methods were investigated sequentially with the same participants on the same afternoon, but the others were investigated on separate days, with some variation in participants between occasions. Ten consultant anaesthetists in a second major hospital were also asked about their usual approach to hand preparation before central venous catheter insertion.

Study procedure

After performing the hand preparation procedure, participants rolled, in turn, four 2-cm segments of a sterile standard Cook triple-lumen central venous catheter between their fingertips, and then dropped each contaminated segment into 10 ml of sterile saline. This was vortexed for 15 s to dislodge adherent microbes. One millilitre of the suspension was then transferred into a Columbia agar pour plate. Bacterial numbers were evaluated by colony counting after 24 h incubation at 37°C.

Statistics

Data were analysed with Systat 7.0 for Windows. Analysis of variance was undertaken using logarithmically transformed means of the four counts from each individual, with group and participant as independent variables ($P \leqslant 0.05$ designated as significant). Post hoc comparisons were made

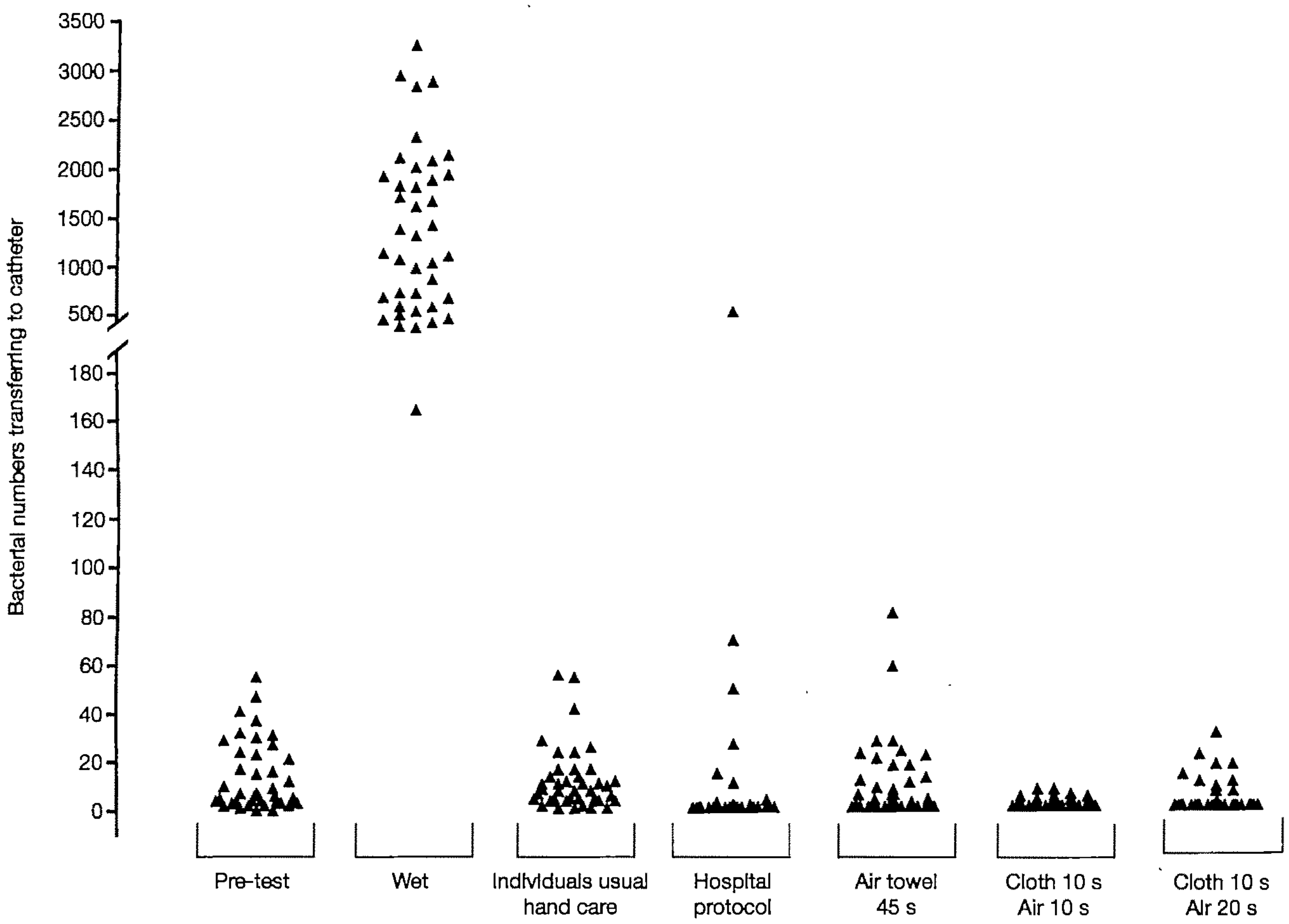

Fig 1 The numbers of bacteria transferred during the seven hand washing methods described in the text (each point relates to one catheter segment).

between the control group ('Pre-test') and each of the other groups, using Fisher's least-significant difference test ($P \leq 0.01$ designated as significant to allow for multiple testing).

Results

Twenty-eight individuals took part in the entire study. Between them, the 10 consultants in the group designated 'Individual' utilized five different hand-washing agents. Only one followed the hospital procedure, and only two used a gown. One anaesthetist used no hand preparation at all. Two participants spent 1 min or more, two spent approximately 30 s, and five spent 15 s or less, washing their hands. Thirty seconds or less was spent on hand drying in all cases, with 15 s or less in five. Six dried their hands on a sterile cloth, and two on an unsterile paper towel. One rinsed with methylated spirits and relied on unaided evaporation for drying. Five out of 10 expressed reluctance to leave an anaesthetized patient with minimal supervision (e.g. a nurse or anaesthetic technician) in order to wash their hands more thoroughly. The 10 consultants questioned in the second major hospital also reported a wide range of hand preparation practices before insertion of central venous catheters. Only six of these reported donning a gown, and two of the six reported following an accepted hospital procedure for hand washing before central venous catheter insertion.

The median, third quartile and maximum number of bacteria transferred to the central venous catheter segments with each method (pooled data, n=40 per group) were, 'Pre-test': 6.5, 24, 55; 'Wet': 1227, 1932, 3254; 'Individual': 7.5, 15, 55; 'Hospital': 0, 1, 500; 'Air-45': 2.5, 15, 80; 'Cloth-air-10': 0, 3, 7; 'Cloth-air-20': 0, 4, 30 (Fig. 1). The difference between groups in the number of bacteria transferred was significant ($P<0.001$). Post hoc comparisons of each group with 'Pre-test' showed that significantly more bacteria were transferred with 'Wet' ($P<0.001$), and significantly fewer with 'Cloth-air-10' and 'Cloth-air-20' (P=0.007 and 0.004, respectively). 'Hospital', 'Individual', and 'Air-45' were not significantly different from 'Pre-test' (P=0.035, 0.73 and 0.176, respectively).

Comment

Our method of selecting participants raises the possibility of sample bias. We addressed this by including participant as an independent variable in the analysis of variance. The finding that the hospital's standard procedure was not significantly different from the control condition (P=0.035) may well be a type II error; the findings in respect of the 'Wet', 'Cloth-air-10' and 'Cloth-air-20' conditions seem secure, particularly given the predominance of counts near zero for 'Cloth-air-10' and 'Cloth-air-20' (Fig. 1). The observations of hand washing practice are consistent with our personal observations within several hospitals in New Zealand and elsewhere.

When 'accepted practice' is routinely violated this usually implies a perception that the violation is harmless and/or that the standard is unreasonable.[5] A perception of harmlessness would no doubt reflect a reliance on sterile gloves. However, wearing a gown has been shown to reduce sepsis in relation to central venous catheter insertion,[6] and glove leaks have been demonstrated in 1.9–5.5% of unused gloves.[7] The perception of unreasonableness is reflected in the expression by five participants of reluctance to leave an anaesthetized patient long enough to carry out a formal hand scrub.

Our data confirm the important role that residual moisture on the hands has in determining the level of bacterial translocation with touch.[1] This factor has not been widely appreciated, and may negate the benefit of conscientious hand washing. The bulk of water can be quickly removed from washed hands using cloth or paper towels, but these tend to leave a film of moisture. This film can be removed by brief hand exposure to a current of hot air, but hot air is relatively inefficient for drying larger amounts of water. Although putting air towels in a clinical environment has been questioned,[8] other evaluations of the use of hot-air dryers in microbiologically sensitive areas are reassuring.[9] The combination of a cloth towel with an air towel seems to offer a method of hand hygiene that is at least as efficacious as formal scrub procedures, but quicker, and therefore, better suited to the pressures of clinical practice and more likely to be adopted routinely.

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References

1 Patrick DR, Findon G, Miller TE. Residual moisture determines the level of touch-contact-associated bacterial transfer following hand washing. *Epidemiol Infect* 1997; **119**: 319–25

2 Larson EL. APIC guideline for handwashing and hand antisepsis in health care settings. *Am J Infect Control* 1995; **23**: 251–69

3 Handwashing Liaison Group. Hand washing: a modest measure—with big effects (Editorial). *BMJ* 1999; **318**: 686

4 Australian and New Zealand College of Anaesthesists. *Policy on Infection Control in Anaesthesia (Policy Document P28)*. Melbourne: The College, 1995

5 Reason J. *Human Error*. New York: Cambridge University Press, 1990

6 Raad II, Hohn DC, Gilbreath BJ, *et al.* Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994; **15**: 231–8

7 Albin MS, Bunegin L, Duke ES, Ritter RR, Page CP. Anatomy of a defective barrier: sequential glove leak detection in a surgical and dental environment. *Crit Care Med* 1992; **20**: 170–84

8 Redway K, Knights B, Johnson K. *A Comparison of the Anti-bacterial Performance of Two Hand Drying Methods (Textile Towels and Warm Air Dryers) After Artificial Contamination and Washing of Hands*. London: University of Westminster, 1995

9 Taylor JH. *The Evaluation of the Performance of World Warm Air Hand Driers*. Chipping Campden: Campden and Chorleywood Food Research Association, 1996. Report No.: FH/24451/2

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BJA

CASE REPORTS

Primary pulmonary hypertension in pregnancy; a role for novel vasodilators

L. Monnery[1]*, J. Nanson[2] and G. Charlton[3]

[1]Department of Anaesthesia, Dorset County Hospital, Williams Avenue, Dorchester DT1 2JY, UK. [2]Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. [3]Shackleton Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK

**Corresponding author*

We describe the case of a 28-week pregnant woman presenting with severe primary pulmonary hypertension (PPH). She had an elective Caesarean section under general anaesthesia at 32 weeks gestation. Pulmonary artery pressures (PAP) measured from a pulmonary artery catheter before anaesthesia were in excess of 100 mm Hg. Intraoperative nitric oxide was used to reduce PAP. After the delivery of a healthy infant PAP was controlled with nebulized iloprost and a prostacyclin infusion. Seven days later she was discharged from intensive care taking an oral calcium antagonist and warfarin. She developed intractable right heart failure and died 14 days after delivery. Despite increasing experience in the use of drugs to reduce PAP, the clinical course of pregnancy complicated by severe PPH is usually fatal.

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The mortality for primary pulmonary hypertension (PPH) complicating pregnancy is very high,[1 2] and the only long-term 'cure' is a heart-lung transplant. Increased pulmonary vascular resistance combined with the normal physiological changes of pregnancy and delivery is difficult to manage. A series from Canada[3] described the successful use of epidurals to manage the delivery of women with pulmonary hypertension from a variety of causes. A successful outcome has also been described following general anaesthesia for Caesarean section in a woman with PPH and coarctation of the aorta.[4] We describe our experience of delivery by Caesarean section under general anaesthetic in a woman with severe PPH.

Case report

A 26-yr-old multiparous woman presented with increasing dyspnoea at 28 weeks of pregnancy. There was no significant past medical history. A pregnancy 3 yr previously had ended in induction of labour at 35 weeks gestation for hypertension and the birth of a healthy daughter.

On examination she had a sinus tachycardia, arterial pressure was 130/80 mm Hg, the jugular venous pressure was 10 cm above the clavicle and there was a parasternal heave. On auscultation she had an accentuated pulmonary component of the second heart sound and a systolic murmur of tricuspid regurgitation. ECG showed right heart strain, and a chest radiograph showed a dilated right heart and prominent pulmonary arteries. An echocardiogram showed normal intra-cardiac anatomy, but a dilated right heart, impaired right ventricular systolic function, tricuspid regurgitation and a right ventricular end systolic pressure of 100 mm Hg. The left heart was normal. A mild microcytic anaemia was present and a ventilation/perfusion scan excluded pulmonary embolic disease.

A clinical diagnosis of PPH was made and she was given heparin, aspirin, ferrous sulphate and intra-muscular dexamethasone to promote foetal lung maturation.

An elective Caesarean section was planned for the 32nd week of pregnancy under general anaesthetic. She was premedicated with temazepam 20 mg, ranitidine 150 mg and metoclopramide 10 mg. In the anaesthetic room she received 0.3 M sodium citrate 30 ml orally, then midazolam 1.5 mg i.v. after which an arterial cannula and pulmonary

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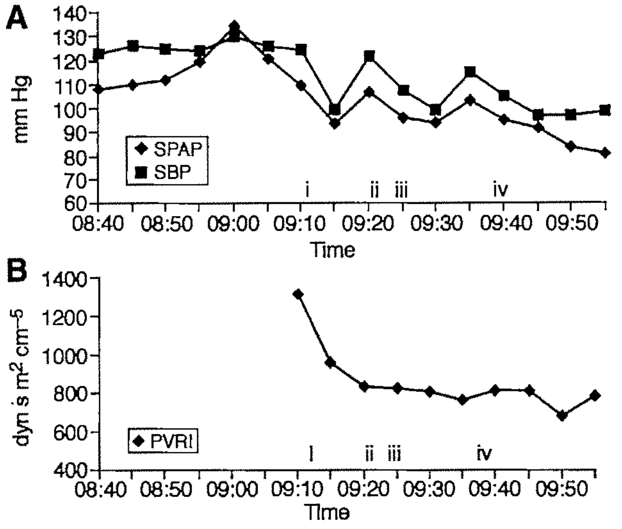

Fig 1 Intra-operative haemodynamic variables showing trends in: (A) systolic pulmonary artery pressures (SPAP) in relation to systemic blood pressure (SBP); and (B) pulmonary vascular resistance index (PVRI) at times (i) induction of anaesthesia, (ii) delivery, (iii) start of nitric oxide, (ii–iv) duration of syntocinon infusion.

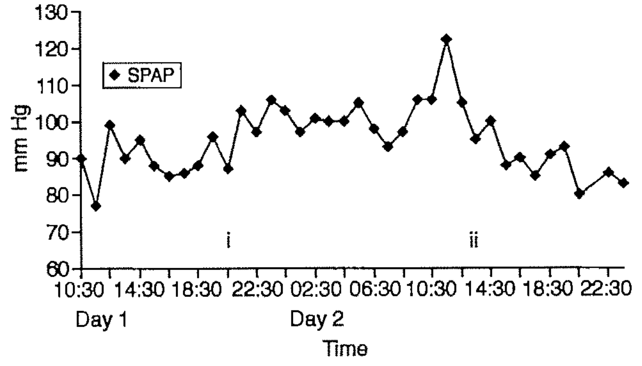

Fig 2 Trends in systolic pulmonary artery pressures (SPAP) during the first 36 h post operation: (i) extubated, nitric oxide stopped, iloprost started; (ii) i.v. prostacyclin started.

artery catheter were inserted. Systolic pulmonary artery pressure (PAP) was equal to systemic pressure at 130 mm Hg. After pre-oxygenation, anaesthesia was induced with propofol 40 mg, fentanyl 1 mg and suxamethonium 100 mg. Cricoid pressure was applied. The trachea was intubated and the lungs ventilated with oxygen and isoflurane. Vecuronium was used for muscle relaxation.

Nitric oxide 1.5 p.p.m. was given after induction of anaesthesia but had to be stopped because of multiple premature ventricular complexes. A live baby boy was delivered 10 min after induction of anaesthesia. He was heavily narcotized but responded rapidly to naloxone. Augmentin 1.2 g i.v. was given after delivery and syntocinon 10 units i.v. as an infusion over 20 min to contract the uterus, which caused only a slight increase in pulmonary artery pressures. Nitric oxide was recommenced after delivery and was well tolerated. The dose was gradually increased to 16 p.p.m. PAP decreased progressively to systolic PA pressures 15 mm Hg below systemic pressures by the end of the procedure (Fig. 1). She was subsequently transferred to intensive care.

Postoperative echocardiography was unchanged. Intravenous heparin was recommenced 4 h post-Caesarean section to maintain an activated partial thromboplastin ratio of 2–2.5. Two hourly nebulized iloprost was introduced. This enabled the nitric oxide and pressure support ventilation to be weaned without any rebound increase in PAP. She was extubated 11 h after surgery. PAP remained at or slightly below systemic pressures (Fig. 2). In an attempt to reduce PAP, the following day an i.v. infusion of prostaglandin I_2 (PgI_2) was started at 2 ng kg^{-1} min^{-1}. The maximum dose of i.v. PGI_2 tolerated was 7.5 ng kg^{-1} min^{-1}, limited by the side effects of headache, flushing, nausea and abdominal cramps. Although cardiac index remained fairly stable (1.9 –3.1) the mixed venous oxygen saturation ($S\bar{v}_{O_2}$) decreased as low as 40% over the subsequent days. Contact with the regional transplant centre had been made preoperatively to discuss timing of a heart-lung transplant. Persistent cardiovascular instability made her unsuitable for early transplantation.

Oral nifedipine 20 mg was given on the 5th postoperative day and increased to 40 mg bd and allowed the i.v. PGI_2 to be reduced. Iloprost nebulizers were given 3–4 hourly and ferrous sulphate was restarted for anaemia (Hb 8.8 g dl^{-1}). On the 8th postoperative day oral anticoagulation with warfarin was commenced and the patient discharged to the ward.

Her course was complicated by recurrent syncope, increasing signs of right ventricular failure with gross peripheral fluid retention. A temporary improvement was achieved with the re-introduction of i.v. PGI_2 and i.v. furosemide but a further syncopal episode resulted in readmission to intensive care. The nifedipine was discontinued and heparin substituted for warfarin. Subclavian central line insertion was complicated by a pneumothorax. The initial chest drain failed to completely re-expand the lung and a second drain was inserted which drained both air and blood. Her condition deteriorated throughout the day. She became progressively more hypoxic and acidotic and died on the 14th postoperative day. Post-mortem examination confirmed right heart failure and unexplained pulmonary hypertension as the cause of death.

Discussion

PPH is defined as a sustained elevation of pulmonary artery pressure (mean greater than 25 mm Hg at rest) in the absence of a demonstrable cause. Pulmonary vasoconstriction, medial hypertrophy, thrombosis in situ and dysfunctional pulmonary vascular endothelium are believed to contribute.[5]

Pulmonary hypertension is tolerated poorly in the parturient. Deterioration typically occurs in the second trimester with symptoms of fatigue, dyspnoea, syncope and chest pain. This corresponds to the physiological increase in cardiac output and blood volume of 40%. During labour, uterine contractions effectively add 500 ml of blood to the circulation. The pain and expulsive effort of labour increase right atrial pressure, blood pressure and cardiac output.[6]

Women with PPH are advised against pregnancy. In early pregnancy a termination is considered. Where PPH is not diagnosed until late in pregnancy an elective delivery is preferred. This facilitates cooperation between specialities, permits monitoring to be started in advance, the pain and haemodynamic consequences of labour to be minimized and an intensive care bed arranged. Premature spontaneous labour is common[2,3] therefore delivery is usually planned for 32–34 weeks gestation. In our patient the cardiovascular physiological changes of pregnancy had already occurred by the time of presentation and some clinical improvement had occurred with oxygen and heparin therapy, so the pregnancy was allowed to continue.

Mangano[7] outlined the principles for management of delivery in these patients as avoidance of increases in pulmonary vascular resistance (PVR) and maintenance of right ventricular preload, left ventricular after-load and right ventricular contractility.

Most reported cases have recommended vaginal delivery under epidural analgesia.[3,8] Pain, oxygen consumption and the haemodynamic consequences of labour can be reduced with epidural analgesia. Epidural diamorphine with low dose bupivacaine gives minimal risk of vasodilatation. However, most describe the management of patients with Eisenmenger's syndrome in whom changes in PVR are better tolerated because the intra-cardiac defect allows the pressure increases to be transmitted to the left side of the heart.

Smedstad has described use of oxytocin both for induction of labour and to increase uterine tone after delivery without apparent haemodynamic consequence.[3] However, oxytocin can cause systemic vasodilatation and low dose infusion has been associated with an acute rise in PVR and fall in cardiac output.[9] Prostaglandin $F_2\alpha$ causes pulmonary vasoconstriction[10] and must be avoided.

An opioid-based general anaesthetic was considered appropriate for a failing right ventricle, not least because the patient refused a regional technique. It facilitated the control of PAP and the use of nitric oxide. Nitric oxide can be administered by facemask but is poorly tolerated, difficult to monitor and cannot be scavenged. A narcotic-based technique minimizes increased pulmonary pressures during laryngoscopy and avoids the excessive negative intropic effect of inhalational agents. Nitrous oxide increases PVR and was omitted. Care was taken to avoid reducing venous return during positive pressure ventilation. Narcotic-related neonatal depression is usually easily managed. O'Hare *et al.*[4] reported a successful outcome following an emergency Caesarean section under general anaesthetic for a woman with PPH and coarctation of the aorta. They employed glyceryl trinitrate intraoperatively and intravenous and aerosolized prostacyclin postoperatively.

Vasoconstriction is a prominent feature, leading to the rationale for using pulmonary vasodilators such as oxygen, nitric oxide, epoprostenol and iloprost in the short term and calcium antagonists in the long term. Nitric oxide has been used in the pre- and post-delivery management of PPH in pregnancy, with clear reductions in PAP as evidenced by cardiac catheterization data,[11] but not during Caesarean section.

Epoprostenol is a naturally occurring prostaglandin and potent vasodilator. It affects vascular remodelling and inhibits platelet aggregation. Iloprost is a synthetic analogue of epoprostenol with improved metabolic and chemical stability, which decreases PAP and PVR, increases cardiac output, and has minimal effect on systemic arterial pressure.[12] The pulmonary vasodilator effect lasts 60–120 min. In comparison, intravenous prostacyclin (epoprostenol) reduces PVR with similar efficacy but reduces systemic arterial pressure to a greater degree[13] with no clinically significant reduction in PAP. Neither iloprost nor prostacyclin is recommended in pregnancy because of concerns over the effect on uterine blood flow. Iloprost is associated with toe deformities in rats.[14]

Patients with PPH are at risk of thrombosis and thromboembolism. The Mayo Clinic group has reported that anticoagulation may improve the outcome in severe pulmonary hypertension.[15]

Pulmonary artery catheterisation provided early warning of rising PAP, deteriorations in right ventricular function and the effects of therapeutic interventions. Its use has not been associated with improved survival[1] and there is an increased risk of pulmonary artery rupture and thrombosis in these conditions.[16]

Excessive systemic dilatation resulting from the nifedipine may have contributed to syncope in our patient. Syncope can also result from ventricular tachyarrhythmias secondary to an ischaemic ventricle, but no such arrhythmias were documented.

Roberts[1] found that the only survivors since 1982 had a cardiac index (CI) >4 litres min^{-1}, right atrial pressure (RAP) <10 cm H_2O and PVR <1000 dyn s^{-1} cm^5. This put our patient into a very high-risk category with CI <4, RAP $\geqslant 10$ and PVR as high as 1142 dyn s^{-1} cm^5. Higgenbottam *et al.*[17] suggest mixed venous oxygen saturation (Sv_{O_2}) as the best prognostic indicator in PPH with a 5 yr survival rate of 17% with $Sv_{O_2}<63\%$ or 55% with an $Sv_{O_2}>63\%$. Sv_{O_2} as low as 40% were recorded in our patient.

PPH complicating pregnancy remains a fatal condition with deaths reported to occur between 2 and 9 days post-delivery,[1] usually from right heart failure. Iloprost and nitric oxide therapies may have a role in controlling PAP in this condition but there is no evidence of improved survival.

References

1 Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy—a lethal combination. *Anaesth Intens Care* 1990; **18**: 366–74

2 Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald. *Heart Disease – a Textbook of Cardiovascular Medicine*, 4th Edn. Saunders, 1992; 1790–1809

3 Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. *Can J Anaesth* 1994; **41**: 502–12

4 O'Hare R, McLoughlin C, Milligan K, McNamee D and Sidhu H. *Anaesthesia* for Caesarean section in the presence of severe primary pulmonary hypertension. *Br J Anaesth* 1998; **81**: 790–2

5 Lewis J, Rubin MD. Primary pulmonary hypertension. *New Engl J Med* 1997; **336**: 111–17

6 Cheek TG, Gutsche BB. Maternal physiological alterations during pregnancy. In: Shnider SM, Levinson G, eds. *Anaesthesia for Obstetrics*, 2nd Edn. Baltimore: Williams & Wilkins, 1987; 3–13

7 Mangano DT. Anaesthesia for the pregnant cardiac patient. In: Shnider SM, Levinson G, eds. *Anaesthesia for Obstetrics*, 3rd Edn. Baltimore: Williams & Wilkins, 1983; 502–8

8 Robinson DE, Leicht CH. Epidural analgesia with low-dose bupivacaine and fentanyl for labor and delivery in a parturient with severe pulmonary hypertension. *Anesthesiology* 1988; **68**: 285–8

9 Takeuchi T, Nishii O, Okamura T, Yaginuma T. Primary pulmonary hypertension in pregnancy. *Int J Gynecol Obstet* 1988; **26**: 145–50

10 Lange AP. Prostaglandins as abortifacients in Denmark. *Acta Obstet Gynecol Scand* 1983; **113** (Suppl): 117–24

11 Robinson JN, Banerjee R, Landzberg MJ, Thiet M. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. *Am J Obstet Gynecol* 1999; **180**: 1045–6

12 Haraldsson A, Kieler-Jenson N, Nathorst-Westfelt U *et al.* Comparison of inhaled nitric oxide and inhaled aerosolised prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *Chest* 1998; **114**: 780–6

13 Scherer T, Radermacher P. Prostacyclin (PGI_2): new aspects of an old substance in the treatment of critically ill patients. *Intensive Care Med* 1997; **23**: 146–58

14 Battenfeld R, Schuh W, Schobel C. Studies on reproductive toxicity of iloprost in rats, rabbits and monkeys. *Toxicol Lett* 1995; **78**: 223–34

15 Fuster V, Steele PM, Edwards WD *et al.* Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984; **70**: 580

16 Barash PG, Nardi D, Hammond G *et al.* Catheter-induced pulmonary artery perforation. *J Thorac Cardiovasc Surg* 1981; **82**: 5–12

17 Higgenbottam T, Butt AY, McMahon A, Westerbeck R, Sharpes L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80**: 151–5

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Central venous catheterization and fatal cardiac tamponade

S. A. Booth[1], B. Norton[2] and D. A. Mulvey[3*]

[1]Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.
[2]Medical Directorate and [3]Critical Care Directorate, Derbyshire Royal Infirmary, London Road, Derby DE1 2QY, UK

**Corresponding author*

Cardiac tamponade is a poorly recognized complication of central venous catheterization associated with a high mortality. We present a case of fatal cardiac tamponade after intrapericardial infusion of total parenteral nutrition in a patient who had two central venous catheters. We suggest that catheter tip position should always be confirmed before use of a catheter. Tamponade should be suspected in a patient who deteriorates when a central venous catheter is used and resuscitation via the catheter should be avoided.

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Complications from central venous catheters are numerous. Cardiac tamponade is a rare but well documented complication that is often fatal. Clinicians fail to consider the diagnosis in patients with typical acute signs and symptoms.[1–5] The time from insertion of the central venous catheter to onset of the clinical features varies from minutes

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to days.[6] Risk factors for the development of cardiac tamponade include incorrect tip position (right atrium and ventricle most common) and infusion of hyperosmolar fluids such as for parenteral nutrition.[1 6–10] We report a patient whose death was shown at post-mortem examination to be caused by tamponade from the infusion of parenteral nutrition. We discuss identification of tip position and question the use of central venous catheters without doing this.

Case report

A 29-yr-old female was admitted with an 8-day history of diarrhoea and vomiting. She was of slight build (weight 47 kg, height 1.65 m), dehydrated, clinically anaemic, and had oral candidiasis. Initial investigations showed marked hypochromic microcytic anaemia (Hb 5.8 g dl^{-1}, MCV 65 fl), leucocytosis (12×10^9 $litre^{-1}$) and thrombocytosis (705×10^9 $litre^{-1}$), hyponatraemia (125 mmol $litre^{-1}$), hypoalbuminaemia (14 g $litre^{-1}$) and a coagulopathy (INR 2.8). Initial treatment included i.v. fluid, blood and coagulation products, vitamin K, and oral nutritional supplementation. Because she was severely malnourished, total parenteral nutrition was considered necessary. A triple lumen central venous catheter was inserted into the right internal jugular vein using the Seldinger technique. Blood was freely aspirated from the vein before and after insertion of the catheter and correct positioning of the catheter tip in the superior vena cava was confirmed by chest radiography.

A diagnosis of ulcerative colitis, toxic megacolon, and spontaneous perforation of the sigmoid colon was made. The patient underwent an emergency subtotal colectomy and ileostomy. On the first day after surgery, parenteral nutrition was re-started via the central venous catheter using an infusion pump. A chest radiograph showed no displacement of the catheter tip.

On the second day after operation, a 16G single lumen cannula ('Leader Cath', Vygon Ltd) was inserted into the left internal jugular vein using the Seldinger technique to act as a dedicated feeding catheter. The position of this line was checked by aspiration of blood, which occurred freely and the pressure trace from a transducer, which was obtained to confirm venous placement. A chest radiograph was ordered, but not taken immediately. The parenteral nutrition was transferred to this cannula and commenced at 90 ml h^{-1} before a radiograph was obtained.

Within 60 min of the change of infusion sites, the patient complained of abdominal, low back and leg pains, and passed bloodstained fluid per rectum. Cardiovascular measurements did not change during this hour. Over the subsequent 30 min, the ECG changed from sinus rhythm at 110 beats min^{-1} to a narrow complex tachycardia of 180–190 beats min^{-1}, and was accompanied by a decrease in systolic arterial pressure from 140 to 90 mm Hg. The central venous pressure measured from the cannula on the right was 9 mm Hg just before the onset of tachycardia, and was unchanged from the previous hour. There were no respiratory symptoms at the onset of tachycardia. The ventilatory frequency was 17 breaths min^{-1} and pulse oximeter saturation 96% while breathing on 2 litre min^{-1} oxygen from a standard mask.

A provisional diagnosis of intra-abdominal haemorrhage was made and rapid i.v. fluids were given whilst medical and surgical opinions were obtained. Urgent chest radiography and echocardiography were arranged. Within 15 min of the onset of tachycardia, the patient became unresponsive with no palpable pulses. Cardiopulmonary resuscitation was commenced but pulseless electrical activity rapidly became asystole and despite prolonged efforts, the patient died. The position of the tip of the left-sided catheter was never documented on a radiograph.

At post-mortem, examination the pericardium contained approximately 200 ml of whitish fluid. Analysis of this fluid showed lipids identical to those in the parenteral nutrition. In comparing the lipid concentrations in the infusion fluid and pericardial fluid, it was concluded that 65 ml of TPN solution had been misplaced. No erosion or perforation of a cardiac chamber or great vessel could be found. All catheters had been removed from the patient before transfer to the mortuary, according to the current standard procedure, so the post-mortem position of the left internal jugular cannula tip could not be confirmed. Gross pulmonary oedema and bilateral pleural effusions were noted, probably caused by acute left ventricular failure and cardiopulmonary resuscitation. The cause of death was attributed to cardiac tamponade from parenteral nutrition infusion.

Discussion

Cardiac tamponade caused by central venous catheters is well documented with more than 100 cases being reported since 1958.[1 7 11] The incidence is not clear from anecdotal and reference-based publications, for two reasons. Reported series have an extremely variable incidence from 0.0001 to 1.4% of all catheter insertions, with no distinction in the literature between feeding and non-feeding catheters. Under reporting of the condition is very likely.[2 8 9 12–14] This rare complication is associated with a very high mortality. Nasim and colleagues[3] noted that before 1980 there was a 77% death rate in cases reported in the English literature. From 1980 to 1989 this was 47%.[3] Other reports give mortality rate of between 65 and 100%.[1 4 6] The current mortality rate is still probably great. Cardiac tamponade can present within minutes of insertion of a central venous catheter to several months later.[6]

The variation in reported incidence and time to presentation is partly related to the many risk factors associated with this complication. Direct trauma at insertion predisposes to vascular or endocardial damage and perforation. The site of insertion and position of the catheter tip are important factors. Cardiac tamponade is more frequent when catheters are inserted via peripheral rather than central veins. This risk could be partly related to the movement of the catheter tip with changes in arm, neck and head position.[1 7 10] Abduction or elevation of the arm of a patient with an antecubital vein catheter advances the catheter tip by up to 7 cm. In adults, the tip of a catheter inserted via the subclavian or internal jugular vein can move by up to 2 cm.[1] Movement is least with catheters inserted via a subclavian vein. Poor skin fixation also predisposes to tip movement.[7] Improved skin fixation may be aided by short 10 or 15 cm long catheters that can be positioned optimally and securely.

The angle that the catheter tip forms with the wall of a vein or cardiac chamber is thought to be an important factor responsible in vessel trauma. When the tip lies at a more perpendicular angle to the wall there is an increased chance of direct trauma and erosion.[6 8] This is particularly relevant when considering catheters inserted via the subclavian veins or left internal jugular vein, as their more tortuous anatomical course increases the chance of direct contact with the constantly moving vessel walls.[15]

Catheter material and design may be an important factor, although cardiac tamponade has been reported with catheters made of flexible material.[1 3 9] Flexible 'Pig-tail' tipped catheters have been shown to significantly reduce the chances of rupture.[13 16]

Early recognition and treatment of cardiac tamponade is essential if mortality is to be avoided. Symptoms and signs are usually sudden and include nausea, dyspnoea, retrosternal chest pain, cyanosis, venous engorgement, pulsus paradoxus, and confusion.[5] The most common findings noted by Nasim and colleagues[3] from case reports were hypotension (88%), raised central venous pressure (70%) and a disturbance in cardiac rhythm (67%), mainly tachycardia. However in 29% of these cases death occurred suddenly after 'vague premonitory signs',[3] as in the present report. Diagnosis of cardiac tamponade is more difficult in sedated ventilated patients, so awareness of catheter-related complications is even more vital.

Investigations may not always assist diagnosis. Signs such as low voltage QRS complexes or electrical alternans may not always be present on an ECG.[5 8] Chest radiographs may not show any abnormalities until considerable fluid has accumulated in the pericardial sac. Transthoracic or transoesophageal echocardiographic investigations are diagnostic.[3 5–7] These techniques are unfortunately not widely available and delaying treatment to obtain these investigations may be fatal. Injection of radio-opaque contrast has also been described for diagnosis of pericardial placement of a catheter tip[1 14] but is not without risk.[17]

Misdiagnosis in cases of cardiac tamponade can lead to a worsening of the clinical condition. Tachycardia and hypotension related to the low cardiac output state may be considered to be caused by hypovolaemia. Giving fluid via the catheter will worsen the condition of the patient. Once the diagnosis has been made, prompt treatment is required. Administration of fluid through the catheter should be stopped, followed by attempted aspiration. If this is unsuccessful then it is appropriate to withdraw the catheter. Failure to improve will require a pericardiocentesis, followed by a thoracotomy if this does not work.[5 6 18] Tragically, diagnosis may only be at post-mortem examination. The pericardial fluid is usually not bloody but of similar composition to that which had been infused. Common sites of perforation are the right atrium and right ventricle (80%) followed by the superior vena cava.[5 11] Perforation has also been reported in the left atrium (patent foramen ovale) and the left pericardiophrenic vein.[10 11] However, there are fatal cases where no evidence of erosion and perforation could be found.[11]

Endocardial injury is thought to be caused by either movement of the catheter tip (e.g. arm movements), by movements of the cardiac chambers and lower superior vena cava (cardiac cycle) or by direct trauma. Injury causes thrombus formation and eventually adherence of the catheter to the endocardium. Erosion occurs which may lead to perforation. Infusion of fluids may then be directly into the pericardial space.[1 19]

Hyperosmolar solutions such as parenteral nutrition increase the risk of erosion and perforation of a vein wall or the endocardium.[6 7 9] Because of this risk, we believe that the distal port of any multi-lumen catheter should not be used for the infusion of hyperosmolar fluid.

Parenteral nutrition solutions may be infused using high-pressure pumps at rates usually exceeding 100 ml h^{-1}. Tamponade can occur with less than 200 ml of any fluid rapidly infused into the pericardial sac. The present report illustrates the dangers of rapid infusion and the risk of giving isosmolar solutions rapidly into the distal port of a catheter. Such practice is common in the operating theatre, in intensive care units, and during resuscitation.[20] Typical checks used in the operating theatre to ascertain the position of a central venous catheter include the easy aspiration and injection of blood and the pressure waveforms measured from the catheter.[18] The present report shows how these may not be reliable signs when used alone.[2] The ECG technique for checking intravascular placement of central venous catheters may be useful when chest radiography cannot be done immediately after catheter insertion (e.g. during surgery), but this will not indicate catheter tip position.[3 21]

In locations other than the operating theatre, chest radiographs are used routinely to check catheter tip position and diagnose other complications of catheter insertion. A radiograph does not confirm i.v. placement, nor exclude extravascular or intra-arterial placement of a catheter,[17] yet it is considered to be an essential step in the prevention of complications.[22–24] We question whether use of a central venous catheter for drug and fluid administration without evidence of tip position is a safe and medico-legally defensible practice during elective surgery. We do not believe that it is acceptable to dismiss chest radiography as impracticable and inconvenient in the operating theatre. Transoesophageal echocardiography allows definitive identification of tip position in the operating theatre,[25] but is rarely available except in cardiac operating theatres. We suggest that pre-operative fluoroscopically guided catheter placement may be the minimal standard for patients undergoing all elective and semi-urgent surgery. Such a change in practice would have significant cost and training implications.[26]

The standard chest radiograph is a guide to tip position only. The 'Greenall Criterion' states that the tip should lie no more than 2 cm below a line joining the lower surfaces of the clavicular heads on a postero-anterior chest radiograph.[18] Many authors have quoted this criterion in their publications.[1 3 5 6 8 11 27] However, in some patients only semi-erect chest radiographs can be obtained, which are subject to geometric or image distortion. As a result the catheter tip can appear to be in a different position.[25] Rutherford and colleagues[4] described this effect and introduced the 'Right Main Bronchus Criterion'. The effects of geometric distortion are markedly reduced, by assuring that the tip lies proximal to the angle formed between the right main bronchus and the trachea. As this anatomical landmark represents the upper limit of the pericardial reflection over the lower superior vena cava,[4 28] there is almost no risk of catheter induced cardiac tamponade. Absence of all risk, however, cannot realistically be achieved as the position of a catheter tip does change with arm, head, neck, and vessel movements. The optimal position for central venous catheter is a complex subject. Catheters placed in the lower superior vena cava or right atrium undoubtedly pose the highest risk of tamponade while those placed higher up, in the upper superior vena cava and brachiocephalic vein, may be associated with a higher incidence of thrombosis and infection.[29]

Another concern is the risk of extravasation of infused fluid via the proximal port of multiple lumen catheters if they are not placed far enough into the great veins.[29 30] To avert this problem only catheters with a proximal lumen opening within 5 cm from the catheter tip should be used and a particular insertion approach should be used. For catheters inserted via the internal jugular vein, the 'high' approach should be used to ensure that more of the catheter is present in the vein. Catheters inserted via the subclavian veins should be inserted as laterally as practically possible. Portable ultrasound probes, some of which incorporate an introducer needle guide, can be used successfully for this goal. We believe that the optimal position for all catheters is above the pericardial reflection, in the upper superior vena cava or brachiocephalic veins. Catheters in the subclavian vein (especially left) and left internal jugular vein have caused concern because of the more perpendicular angle with which the tip may lie compared with the vessel wall. In this situation, flexible or 'Pig-tail' tipped catheters may be of enormous benefit.[13 29]

The correct length of catheter to be inserted is also a contentious issue. Studies using right atrial electrocardiography or formulae based on patient weight can reduce the risk of tip malposition.[27 30] Chalkiadis and Goucke recently concluded that no particular depth of insertion could be recommended, and stated that the 'depth of insertion should be determined in a similar fashion to the placement of an epidural catheter where the skin-to-space distance is measured. Provision within catheter insertion kits of a venepuncture needle with graduations every one centimetre would facilitate this technique'.[30]

This report illustrates the need to maintain a high level of awareness about catheter-tip position, even when preventive practices suggest it is sited correctly. Cardiac tamponade must be considered in any patient with an indwelling central venous catheter who shows evidence of clinical deterioration, however vague the symptoms and signs. Resuscitation using the catheter should be avoided until cardiac tamponade has been excluded.

References

1 Collier PE, Ryan JJ, Diamond DL. Cardiac tamponade from central venous catheters. Report of a case and review of the English literature. *Angiology* 1998; **35**: 595–600

2 Goutail-Flaud MF, Sfez M, Berg A, *et al.* Central venous catheter-related complications in newborns and infants: a 587-case survey. *J Pediatr Surg* 1991; **26**: 645–50

3 Nasim A, Cooper GG, Ah-See AK. Cardiac tamponade due to central venous catheterization. *J R Coll Surg Edinb* 1992; **37**: 337–9

4 Rutherford JS, Merry AF, Occleshaw CJ. Depth of central venous catheterization: an audit of practice in a cardiac surgical unit. *Anaesth Intensive Care* 1994; **22**: 267–71

5 Chamsi-Pasha H, Waldek S. Cardiac tamponade complicating central venous catheter. *Postgrad Med J* 1988; **64**: 290–1

6 Cherng Y-G, Cheng Y-J, Chen T-G, Wang C-M, Liu C-C. Cardiac tamponade in an infant – a rare complication of central venous catheterization. *Anaesthesia* 1994; **49**: 1052–4

7 Sutcliffe AG. Total parenteral nutrition tamponade. *J R Soc Med* 1995; **88**: 173–4

8 Jihn JG, Weinberg GL, Laurito CE. Intraoperative cardiac tamponade after central venous cannulation. *Anesth Analg* 1996; **82**: 664–5

9 Greenspoon JS, Masaki DI, Kurz CR. Cardiac tamponade in pregnancy during central hyperalimentation. *Obstet Gynecol* 1989; **73**: 465–6

10 van Haeften TW, van Pampus EC, Boot H, Strack van Schijndel RJ, Thijs LG. Cardiac tamponade from misplaced central venous line in pericardiophrenic vein. *Arch Intern Med* 1988; **148**: 1649–50

11 Collier PE, Goodman GB. Cardiac tamponade caused by central venous catheter perforation of the heart: A preventable complication. *J Am Coll Surg* 1995; **181**: 459–63

12 Bagwell CE, Salzberg AM, Sonnino RE, Haynes JH. Potentially lethal complications of central venous catheter placement. *J Pediatr Surg* 2000; **35**: 709–13

13 Merry AF, Webster CS, van Cotthem IC, Holland RL, Beca JS, Middleton NG. A prospective randomized clinical assessment of a new Pigtail central venous catheter in comparison with standard alternatives. *Anaesth Intensive Care* 1999; **27**: 639–45

14 Robinson JF, Robinson WA, Cohn A, Garg K, Armstrong JD 2nd. Perforation of the great vessels during central venous line placement. *Arch Intern Med* 1995; **155**: 1225–8

15 Sheep RE, Guiney WB Jr. Fatal cardiac tamponade. Occurrence with other complications after internal jugular vein cannulation. *JAMA* 1982; **248**: 1632–5

16 Belani KG, Wilder RT, Campbell LM, Amplatz K, Buckley JJ. The new "Pig-tail" tipped central venous catheter—a design to eliminate vascular perforation. *Anesth Analg* 1989; **68**: S20

17 Losert H, Prokesch R, Grabenwoger M, *et al.* Inadvertent transpericardial insertion of a central venous line with cardiac tamponade failure of preventive practices. *Intensive Care Med* 2000; **26**: 1147–50

18 Greenall MJ, Blewitt RW, McMahon MJ. Cardiac tamponade and central venous catheters. *BMJ* 1975; **2**: 595–7

19 Edwards H, King TC. Cardiac tamponade from central venous catheters. *Arch Surg* 1982; **117**: 965–7

20 Basket PJF. Hypovolaemic shock. In: Skinner D, Driscoll P, Earlam R, eds. *ABC of Major Trauma*. London: BMA, 1996; 22–27

21 Hoffmann MA, Langer JC, Pearl RH, Filler RM. Electrocardiograph guided placement of central venous catheters (surgical workshop). *Br J Surg* 1989: **76**: 1032–3

22 Silk DBA. *Nutritional Support in Hospital Practice*. Oxford: Blackwell Scientific Publications, 1983

23 Rosen M, Latto IP, Shang W. *Handbook of Percutaneous Central Venous Catheterisation*, 2nd Edn. WB Saunders, 1992

24 Otto CW. Central Venous Pressure Monitoring. In: Blitt CD, ed. *Monitoring Anaesthesia and Critical Care Medicine*, 2nd Edn. Churchill Livingstone, 1990

25 Andropoulos DB. Transesophageal echocardiography as a guide to central venous catheter placement in pediatric patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; **13**: 320–1

26 Kishen R. Central venous pressure monitoring during anaesthesia and surgery. In: Gray AJG, Hoile RW, Ingram GS, Sherry KM, eds. *The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997*

27 Peres PW. Positioning central venous catheters—a prospective survey. *Anaesth Intensive Care* 1990; **18**: 536–9

28 Schuster M, Nave H, Piepenbrock S, Pabst R, Panning B. The carina as a landmark in central venous catheter placement. *Br J Anaesth* 2000; **85**: 192–4

29 Fletcher SJ, Bodenham AR. Safe placement of central venous catheters: where should the tip of the catheter lie? *Br J Anaesth* 2000; **85**: 188–191

30 Chalkiadis GA, Goucke CR. Depth of central venous catheter insertion in adults: an audit and assessment of a technique to improve tip position. *Anaesth Intensive Care* 1998; **26**: 61–6

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Ruptured superior thyroid artery from central vein cannulation: treatment by coil embolization

V. Jeganath[1]*, J. G. McElwaine[2] and P. Stewart[2]

[1]Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK. [2]Directorate of Anaesthesia and Intensive Care, City General, Newcastle Road, Stoke-on-Trent ST4 6QG, UK.

**Corresponding author*

Central vein cannulation is associated with several complications, some of which may be fatal. This case report describes a life-threatening complication after insertion of a central venous line. An obese female patient with end-stage renal failure due to nephrotic syndrome developed a huge neck swelling and sudden airway obstruction after attempted cannulation of the internal jugular vein for haemodialysis. Tracheal intubation was achieved using a gum-elastic bougie. Investigations revealed abnormal blood clotting. The coagulopathy was treated, but the neck swelling continued to increase in size. Carotid angiography showed a ruptured right superior thyroid artery. The haemorrhage was controlled by coil embolization of the artery. This case report demonstrates the usefulness of the gum-elastic bougie in the presence of a difficult airway and of interventional radiology in the management of vascular accidents.

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It is well known that central vein cannulation is associated with various complications such as carotid artery injury, arterial cannulation,[1] injury to the thoracic duct[2] and pericardial tamponade,[3 4] some of which can be life-threatening. This case report illustrates the management of ruptured superior thyroid artery and airway obstruction after attempted cannulation of the internal jugular vein.

Case report

A 44-yr-old, obese (120 kg) woman was admitted with nephrotic syndrome and end-stage renal failure. She was found to be anaemic (Hb 8 g dl^{-1}) and thrombocytopaenic (84×10^9 platelets $litre^{-1}$). Bone marrow biopsy suggested early small lymphocytic lymphoma. Treatment included steroids, chlorambucil and frusemide.

After 3 days, the patient required haemodialysis as her serum urea and creatinine concentrations were elevated (urea, 41 mmol $litre^{-1}$; creatinine, 587 μmol $litre^{-1}$). Insertion of a haemodialysis catheter was attempted via the internal jugular vein. After two unsuccessful attempts on the right side and one on the left, the dialysis catheter was inserted via the right femoral vein.

After the procedure, the patient developed a rapidly enlarging swelling round the neck. Two hours later, the patient was referred to the anaesthetic team for assessment of her airway. On examination, the patient was conscious and orientated but anxious. The neck swelling was huge and firm. It extended round the neck and up to the ears. The patient's cardiovascular condition was stable. Sp_{O_2} was 93% on air. There was no evidence of stridor and the patient's chest was clear to auscultation. However, the patient was drooling saliva and had dysphagia and hoarseness because of compression of the neck veins by the swelling with oedema and obstruction in the pharynx and larynx. After discussion with the consultant anaesthetist, it was felt that the safest course would be to transfer the patient to the operating theatre, as difficulty with intubation was anticipated and an attempt at awake fibre-optic intubation was planned. It was also planned to have a full range of equipment available for managing difficult airways.

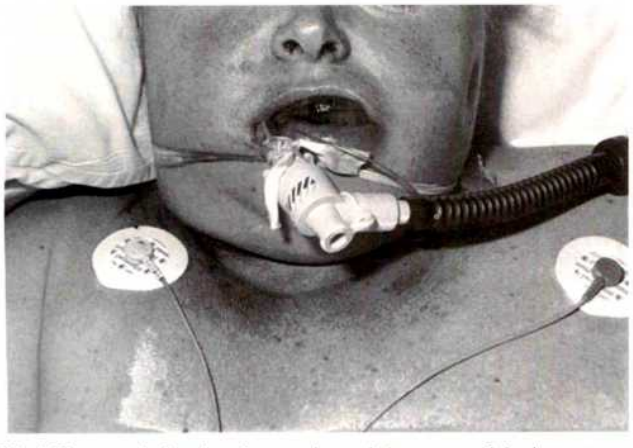

Fig 1 Photograph showing the severity and the extent of the haematoma. Note the swollen tongue.

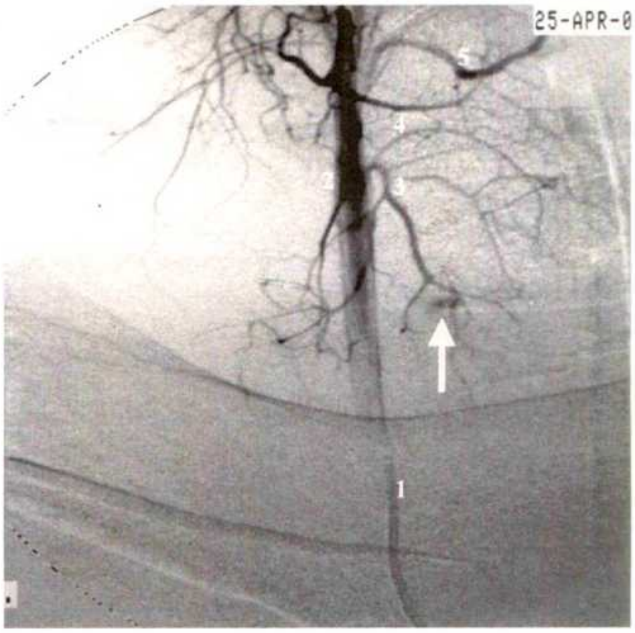

Fig 2 Angiogram of the right external carotid artery (postero-anterior view) showing the characteristic 'blush' appearance of the ruptured superior thyroid artery, the first branch of the external carotid artery. Note the other features: 1, angiography catheter; 2, right external carotid artery; 3, superior thyroid artery; 4, lingual artery; 5, facial artery

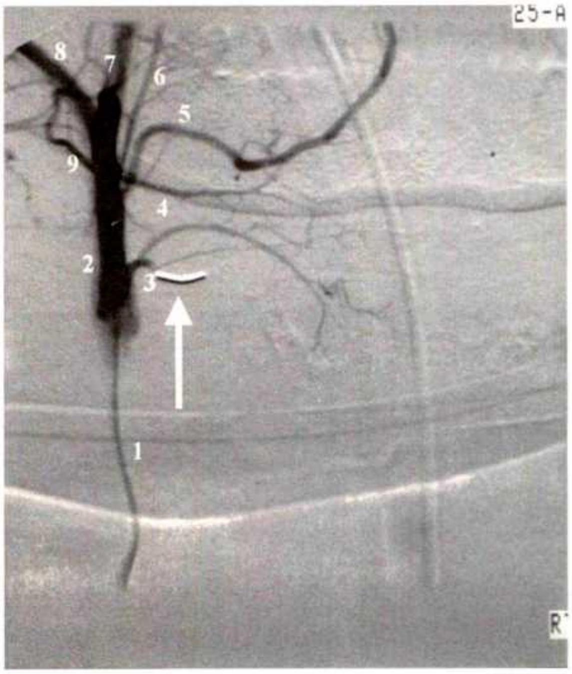

Fig 3 Angiogram (postero-anterior view) showing the intra-arterial coil in the superior thyroid artery after haemostasis had been achieved. Note the other features: 1, angiography catheter; 2, right external carotid artery; 3, superior thyroid artery; 4, lingual artery; 5, facial artery; 6, ascending pharyngeal artery; 7, maxillary artery; 8, superficial femoral artery; 9, occipital artery.

An operating theatre was organized and the patient immediately transferred there from the ward. During the transfer, the patient developed sudden airway obstruction, became cyanosed and had a cardiorespiratory arrest. Cardiopulmonary resuscitation was commenced. On arrival in the anaesthetic room, epinephrine 1 mg was administered intravenously and resuscitation was continued. Direct laryngoscopy was performed but no landmarks (including the epiglottis) could be seen because of the oedematous soft tissue swelling. A 7 mm tracheal tube was passed blindly but failed to enter the trachea. A gum-elastic bougie was then passed blindly through the soft tissue and an 8 mm tracheal tube was 'railroaded' over the bougie. The tube was confirmed to be in the trachea by capnography. Cardiac output was restored on establishing artificial ventilation. The patient made spontaneous attempts to breathe, but was sedated, paralysed and transferred to the intensive care unit for further management.

In the intensive care unit, the patient was positioned with head-up tilt and dexamethasone 8 mg was given. Investigations showed abnormal blood clotting (international normalized ratio, 1.8; activated partial thromboplastin time ratio, >5 (the normal range is 0.8–1.17); Hb, 6 g dl^{-1}) and it was realized that the patient had received heparin 5000 i.u. intravenously before insertion of the haemodialysis catheter. Red blood cells, fresh frozen plasma and protamine sulphate 50 mg were given. Coagulation tests were repeated after 2 h and were within the normal range. However, the neck swelling continued to increase in size, extending to the chest, shoulders and occiput (Figure 1). Chest x-ray showed a widened mediastinum.

A contrast computerized tomography (CT) scan was performed in an attempt to identify the source of haemorrhage, but the result was inconclusive. Carotid angiography was then performed by passing the angiography catheter up the right femoral artery. This revealed bleeding from a ruptured right superior thyroid artery (Figure 2). Coil embolization was performed by an interventional radiologist and haemostasis was achieved (Figure 3).

The patient required ventilatory support for the next 4 days, during which time haemodialysis was commenced. The neck swelling gradually reduced in size. The trachea was extubated uneventfully after 4 days and the patient was discharged to the ward.

Discussion

Various complications of central vein cannulation have been described, including pneumothorax, chylothorax,[2] carotid artery injury, stroke,[5] arteriovenous fistulae, pseudoaneurysms,[6] arrhythmias,[7] azygos arch cannulation,[8] acute airway obstruction,[9] diaphragmatic paralysis,[10] nerve injury,[11] blindness,[12] ventricular perforation and cardiac tamponade.[3 4 12] Some of these complications may be fatal. We have found no other report of a case of ruptured superior thyroid artery after central venous line insertion.

Though the abnormal clotting profile was not the main cause of bleeding in this case, we feel that it would have been a compounding factor in the rapid progression of the neck haematoma. This emphasizes the desirability of ensuring normal clotting function before attempting to cannulate the central vein.

Ultrasound-guided insertion of a central line has been shown to be safe and reliable, and can minimize several of the complications associated with central venous puncture.[13 14] The technique may be especially beneficial in high-risk patients, e.g. those with coagulation defects (inherited and acquired), obesity or haemodynamic instability. Moreover, inability to position the patient in the supine or Trendelenburg position (e.g. because of head injury or high intracranial pressure) or inability to rotate the neck (e.g. in patients with cervical spine injury) make insertion of a central line technically difficult with an increased risk of complications. It has been shown that ultrasound guidance increases the success rate and reduces the complication rate of central venous access in patients at high risk of complications or with unusual anatomy.[15] We, therefore, recommend that the technique should be adopted to gain central venous access in difficult and high-risk cases.

This case highlights the importance of recognizing impending airway obstruction and the need for prompt referral to the anaesthetic team.

The management of patients with obstructed airway has been criticized in recent years[16] and it is suggested that each patient should be managed according to the level and nature of the obstruction and the clinical circumstances.[17] Fibreoptic intubation may not be the answer for every airway problem and anaesthetists should be able to use other options. There have been several case reports where the gum-elastic bougie has been helpful in managing the difficult airway.[18–20] It has also been shown that tracheal intubation can be achieved more quickly and safely with the help of the bougie[21]. Although the gum-elastic bougie is commonly used in the UK, it is seldom used in the USA.[22] We believe that rapid tracheal intubation in our patient could not have been achieved by any other means. Similar circumstances may arise from a haematoma following carotid artery surgery, thyroid surgery, cervical spine surgery, radical neck dissection or trauma. The gum-elastic bougie may be useful in such circumstances and we recommend that every anaesthetist should be familiar with it.

Finally, this case illustrates the successful management of ruptured superior thyroid artery by interventional radiology. Though surgical exploration was considered as a means of controlling the haemorrhage, the surgeons were not sure whether the haemorrhage was from the right or left side of the neck. Moreover, the chest x-ray showed a widened mediastinum which raised the suspicion of possible injury to a major blood vessel such as the arch of the aorta, innominate vessels or subclavian vessels. Carotid angiography was helpful in the diagnosis and treatment of the haematoma. Cases of vascular accidents and intractable haemorrhage have been managed by coil embolization.[23 24] We feel that this appears to be a rapid and effective method of treating vascular accidents and can be particularly helpful in cases with difficult diagnoses.

References

1 Wang RC, Katz SE, Lubow M. Visual loss and central venous catheterization: cortical blindness and homonymous hemianopsia after inadvertent subclavian artery entry. *J Neuroopthalmol* 2000; **20**: 32–4

2 Hsu LH, Lien TC, Wang JH. Chylothorax: a complication of internal jugular vein catheterization. *Chung Hua I Hsueh Tsa Chih (Taipei)* 1997; **60**: 57–61

3 Cavatorta F, Campisi S, Fiorini F. Fatal pericardial tamponade by a guide wire during jugular catheterization. *Nephron* 1998; **79**: 352

4 Hamilton DL, Jackson RM. Haemopericardium: a rare fatal complication of attempted subclavian vein cannulation. A report of two cases. *Eur J Anaesthesiol* 1998; **15**: 501–4

5 Mainland PA, Tam WH, Law B, Kee WN. Stroke following central venous cannulation. *Lancet* 1997; **349**: 921

6 Tarng DC, Huang TP, Lin KP. Brachial plexus compression due to subclavian pseudoaneurysm from cannulation of jugular vein haemodialysis catheter. *Am J Kidney Dis* 1998; **31**: 694–7

7 Keohane M, Allen R. Persistent atrial fibrillation following central venous cannulation. *Paediatr Anaesth* 1999; **9**: 178–9

8 Bankier AA, Mallek R, Wiesmayr MN, *et al.* Azygos arch cannulation by central venous catheters: radiographic evidence of malposition and subsequent complications. *J Thoracic Imag* 1997; **12**: 64–9

9 Lo WK. Neck haematoma and airway obstruction in a pre-eclamptic patient: a complication of internal jugular vein cannulation. *Anaesth Intens Care* 1997; **25**: 423–5

10 Akata T, Noda Y, Nagata T, Noda E, Kandabashi T. Hemidiaphragmatic paralysis following subclavian vein catheterisation. *Acta Anesthesiol Scand* 1997; **41**: 1223–5

11 Karakaya D, Baris S, Güldogus F, Incesu L, Sarihasan B, Tür A. Brachial plexus injury during subclavian vein catheterization for haemodialysis. *J Clin Anesth* 2000; **12**: 220–3

12 Porter JM, Page R, Wood AE, Phelan D. Ventricular perforation associated with central venous introducer–dilator systems. *Can J Anaesth* 1997; **44**: 317–20

13 Slama M, Novara A, Safavian A, Ossart M, Safar M, Fagon JY. Improvement of internal jugular vein cannulation using an ultrasound-guided technique. *Intensive Care Med* 1997; **23**: 916–19

14 Geddes CC, Walbaum D, Fox JG, Mactier RA. Insertion of internal jugular temporary haemodialysis cannulae by an ultrasound guidance—a prospective comparison of experienced and inexperienced operators. *Clin Nephrol* 1998; **50**: 320–5

15 Fry WR, Clagett GC, O'Rourke PT. Ultrasound-guided central venous access. *Arch Surgery* 1999; **134**: 738–40

16 Gray AJG, Hoile RW, Ingram GS, Sherry K. *The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997*. London: NCEPOD, 1998

17 Mason RA, Fielder CP. The obstructed airway in head and neck surgery. *Anaesthesia* 1999; **54**: 625–8

18 Benson PF. The gum-elastic bougie: a life-saver. *Anesth Analg* 1992; **74**: 318

19 Koay CK. Difficult tracheal intubation—analysis and management in 37 cases. *Singapore Med J* 1998; **39**: 112–4

20 Williamson JA, Webb RK, Szekely S, Gillies ER, Dreosti AV. The Australian Incident Monitoring Study. Difficult intubation: an analysis of 2000 incident reports. *Anaesth Intensive Care* 1993; **21**: 602–7

21 Nolan JP, Wilson ME. An evaluation of the gum-elastic bougie: intubation times and incidence of sore throat. *Anaesthesia* 1992; **47**: 878–81

22 McCarroll SM, Lamont BJ, Buckland MR, Yates APB. The gum-elastic bougie: old but still useful. *Anesthesiology* 1988; **68**: 643–4

23 Wunschel-Joseph ME, Gottwalles Y, Weisse D, Hanssen M. Rupture of a branch of the pulmonary artery during Swan–Ganz catheterization—treatment by coil embolization. *Arch Mal Couer Vaiss* 1999; **92**: 259–63

24 Gujral S. Internal iliac artery embolization for intractable bladder haemorrhage in the perioperative phase. *Postgrad Med J* 1999; **75**: 167–8

British Journal of Anaesthesia **87** (**2**): 306–8 (2001)

Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine–sulphadiazine-coated central venous catheter

R. Stephens[1], M. Mythen[1], P. Kallis[1], D. W. L. Davies[1]*, W. Egner[2] and A. Rickards[3]

[1]UCL Hospitals, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK. [2]Supraregional Protein Reference Unit, Department of Immunology, Northern General Hospital NHS Trust, Sheffield S5 7YT, UK. [3]The Heart Hospital, 50 Wimpole Street, London W1M 7DG, UK

**Corresponding author*

Chlorhexidine allergy has been described in the literature, mainly in Japanese individuals. Most reactions have been limited to the skin, mild in severity and a result of chlorhexidine containing solutions such as 'Savlon' (Novartis Consumer Health, Horesham, UK). We describe what we believe is the first reported case of anaphylaxis in a European patient to a chlorhexidine-sulphadiazine-coated central venous catheter.

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Keywords: allergy; complications, anaphylaxis; complications, chlorhexidine allergy; equipment, catheters central venous

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Allergy to chlorhexidine is described in the literature, mainly in Japanese individuals. Most reactions have been limited to the skin, mild in severity and a result of chlorhexidine-containing solutions such as 'Savlon' (Novartis Consumer Health, Horesham, UK). In 1997, reports appeared of anaphylaxis in Japanese individuals to a chlorhexidine–sulphadiazine-coated central venous catheter.[1 2]

We describe what we believe to be the first reported case of anaphylaxis in a European patient to a chlorhexidine–sulphadiazine-coated central venous catheter.

Case report

A 50-yr-old man with a history of ischaemic heart disease presented for coronary artery bypass graft surgery. He had been diagnosed with Type II diabetes in 1992 and had undergone two percutaneous coronary angioplasties for coronary artery disease. His most recent coronary angiogram showed recurrent two-vessel disease with good left ventricular function. There was no other significant past medical or surgical history and he was a non-smoker.

He had been told that he was 'sensitive' to penicillin and was taking diltiazem and gliclazide. On further questioning, he felt that the skin antiseptic fluid used for his angiogram, performed abroad, had resulted in an itchy rash in his groin, for which he had been prescribed an oral antihistamine, cetirizine. It was thought likely that this was the antiseptic solution 'Savlon' which contains chlorhexidine.

Clinical examination was unremarkable, and he was premedicated with temazepam and atenolol on the day of surgery. In the anaesthetic room large bore i.v. access and invasive monitoring was established following midazolam sedation. The patient was pre-oxygenated and 1 litre of Hartmann's solution was infused i.v. during induction of anaesthesia. Anaesthesia was induced with midazolam, fentanyl, and propofol and maintained with an air/oxygen/isoflurane mixture. Neuromuscular paralysis was achieved with pancuronium and the airway was secured with a Portex endotracheal tube. A central venous catheter (Arrow-Howes™ Quad-lumen Central Venous Catheterization Set with ARROWg$^+$ard Blue® Catheter, Arrow, Reading USA), was inserted in the right internal jugular vein following skin preparation with aqueous iodine ('Betadine', Seton Scholl Healthcare, Oldham, UK). Simultaneously, a urethral catheter was placed after cleansing the urethral meatus with 'Savlon' solution.

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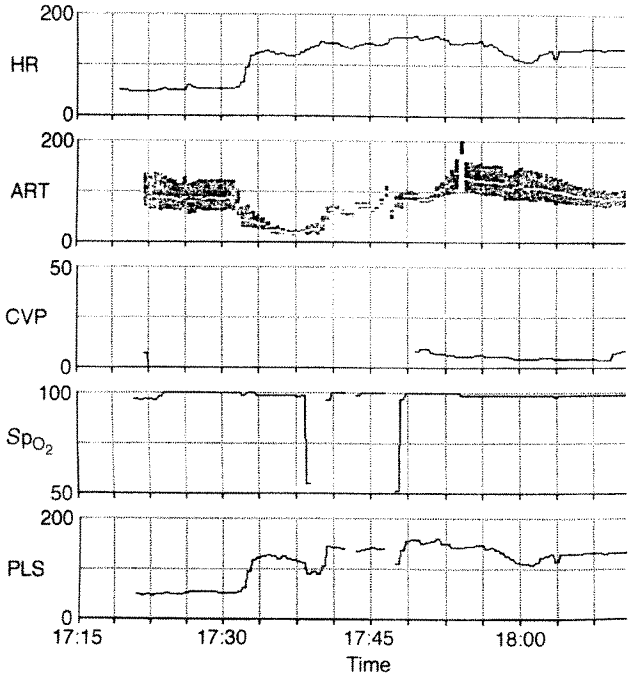

Fig 1 Heat rate (HR) and arterial pressure (ART) changes during the first episode of anaphylaxsis.

After 1–2 min the patient developed a widespread erythematous rash, periorbital oedema and became progressively hypotensive (Fig. 1), culminating in pulseless electrical activity. 100% Oxygen and external cardiac massage were commenced immediately and continued until a return of pressure was recorded on the invasive arterial trace after 10–15 min. The patient did not develop significant bronchospasm. During the cardiac arrest a total of 1 mg phenylephrine, 10 mg adrenaline (in increasing increments), 10 ml 10% $CaCl_2$ and 4 litres of fluid were given. Subsequent treatment included 10 mg chlorpheniramine, 200 mg hydrocortisone and 50 mg ranitidine. The patient had not been given any antibiotics at this stage. Surgery was abandoned and the patient was transferred to the intensive care unit for further monitoring. At this stage, the precipitating drug was thought to be the 'Savlon' used before urethral catheterization. The patient was sedated and ventilated for 18 h in the Intensive Care Unit, after which the sedation was stopped and his trachea subsequently extubated uneventfully.

Blood obtained 1 h post-cardiac arrest revealed a markedly elevated serum tryptase at 157 mg litre^{-1} (normal range 0–12 mg litre^{-1}), C reactive protein of 7 mg litre^{-1} (range 0–6 mg litre^{-1}) and normal complement levels. The patient was discharged home after 4 days observation, neurologically intact with no evidence of long term cardiovascular sequelae.

Skin testing, to propofol, fentanyl, pancuronium, natural rubber latex (three preparations), midazolam, and aqueous betadine were all negative. No reaction was seen to 0.04% chlorhexidine but a large weal with pseudopods measuring 7×7 mm with a 14×14 mm flare was seen with 0.4 and 4% dilutions. This was considered to be a positive result as no reaction was seen in two control subjects at any concentration. A provisional diagnosis was made of IgE mediated allergy to chlorhexidine, present in 'Savlon', and avoidance of chlorhexidine antisepsis was advised.

Three weeks later, the patient was rescheduled for a second attempt at coronary artery surgery. This time, it was decided to avoid chlorhexidine containing products, to prospectively give steroids along with H_1/H_2 antagonists, and to administer drugs and insert lines one by one so as to identify more easily the cause of any deterioration. Two doses of 20 mg prednisolone and three doses of 20 mg methylprednisolone were given orally at 6 h intervals in the 30 h before surgery. He also received 4 mg chlorpheniramine and 150 mg ranitidine, together with his normal medication of glicazide and diltiazem. The patient was again premedicated before surgery, but on this occasion was given morphine and hyoscine.

Two consultant anaesthetists conducted anaesthesia on this occasion. The patient was transferred to the anaesthetic room and monitored with an electrocardiograph and pulse oximetry. A radial artery was cannulated and transduced, and a large bore i.v. cannula was sited under lignocaine local anaesthesia. Anaesthesia was again induced with midazolam and fentanyl, and neuromuscular paralysis was achieved with rocuronium. A further 100 mg hydrocortisone was given at induction of anaesthesia. The airway was secured with a Portex endotracheal tube, and the arterial pressure was noted at 160/80 mm Hg, with a heart rate of 80 beats min^{-1}, in sinus rhythm. A central venous catheter was placed in the right internal jugular vein after cleaning with aqueous iodine solution ('Betadine'). Whilst flushing the central venous line with heparinized saline, progressive hypotension was again noticed to occur, culminating in pulseless electrical activity cardiac arrest, accompanied by facial oedema and an erythematous rash. The central venous line was removed immediately, replaced with a single lumen cannula (14G Abbocath), and 100% oxygen and external cardiac massage commenced. During the cardiac arrest, 10 mg phenylephrine, 4 mg adrenaline, and 3 mg noradrenaline were required, and 10 ml 10% $CaCl_2$, 200 mg lignocaine (for two episodes of ventricular tachycardia), 2 M units of aprotinin (in case of C-1-esterase deficiency) and 10 mg chlorpheniramine. Atrial fibrillation was noted on the ECG. The patient again received a total of 4 litre of i.v. fluid. Surgery was further postponed and the patient transferred to the Intensive Care Unit. Two hours later, he remained in atrial fibrillation at a rate of 130 beats min^{-1}, and his ECG showed evidence of some non-specific ST depression. He was, therefore, DC cardioverted with a single 50 J shock. The ST segments were noted to normalize on return to sinus rhythm.

Blood obtained 1 h post-operatively showed a serum tryptase level of 68 mg litre^{-1}, total creatine kinase 33 iu litre^{-1} (reference range 33–186 iu litre^{-1}) and creatine kinase MB fraction 2 iu litre^{-1} (range 0–24 iu litre^{-1}). The post-operative ECG was unchanged. At 24 h, the total CK was 33 iu litre^{-1} and the CK-MB still normal at 5 iu litre^{-1}. The patient's trachea was extubated after 12 h and the patient discharged home 2 days later. He was again neurologically intact showing no physical signs of long term sequelae.

In response to further skin testing, the patient was positive to chlorhexidine at 4% and 0.4% as before, but where previously negative he was now skin test positive at 0.04%. His angina is currently being managed medically.

Discussion

Chlorhexidine allergy has been well described for over 30 yrs in European and Japanese individuals, mainly as a result of application to skin or mucus membranes before instrumentation.[3–6]

Although unusual, we feel that anaphylaxis to chlorhexidine is the most likely cause for this patient's clinical course on both occasions for a number of reasons. Sudden hypotension (which was resistant to treatment), tachycardia and widespread erythematous rash, are all features of an acute severe anaphylactic or anaphylactoid reaction.[7] Elevated serum tryptase (>10 µg litre^{-1}) is a relatively sensitive (86%), and specific (88%) indicator of anaphylaxis and anaphylactoid reactions.[8 9] Skin prick testing was positive for chlorhexidine, and negative to all administered anaesthetic agents including natural rubber latex. The central venous catheter was subsequently examined and found to be chlorhexidine coated, with a warning on the packaging urging extreme caution in chlorhexidine sensitive patients.

There are several interesting features of this case. First, on both occasions (and in the case report by Oda and colleagues[2]), the patient was easy to ventilate—implying that there was little or no bronchospasm. Contrary to common belief, a recent review of clinical and laboratory markers of anaphylaxis and anaphylactoid reactions found that bronchospasm was a feature in only 43% of patients with allergy-proven anaphylaxis, and in 28% of those having anaphylactoid reactions.[10] Second, large doses of vasopressors were needed in both episodes to restore the arterial pressure, presumably as a result of the profound vasodilatation secondary to mediator release. It was extremely fortunate that the patient was being invasively monitored at the time of anaphylaxis. Third, as it is not widely appreciated that central lines may be pre-coated with chlorhexidine and (as is routine practice) the line was handed to us already open, none of us thought to check the package insert.

Anaphylaxis has previously been reported to chlorhexidine–sulphadiazine-coated central venous catheters in two Japanese individuals, both of whom received coated central venous catheters on two occasions.[1 2] Interestingly in one report[2] skin prick testing after the first anaphylactic episode was negative to chlorhexidine, but the second test at 6 weeks was positive. Unfortunately, this result was not reported to the anaesthetists, resulting in a second exposure and anaphylaxis. The optimal time to skin prick test is uncertain, but most allergists wait 6–12 weeks after the episode in order to avoid false negative results.[11]

Products containing chlorhexidine are widely used in medicine and surgery. In our experience both doctors and nurses are often unaware that chlorhexidine is present, as we were on this occasion. This may have serious life-threatening consequences despite the warnings being marked on the product packaging.

References

1 Terazawa E, Nagase K, Masue T, *et al.* Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. *Masui* 1998; **47**: 556–61

2 Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central venous catheter. *Anesthesiology* 1997; **87**: 1242–44

3 Chisholm DG, Calder I, Peterson D, Powell M, Moult P. Intranasal chlorhexidine resulting in anaphylactic circulatory arrest. *BMJ* 1997; **315**: 785

4 Okano M, Nomura M, Okada N, Sato K, Tashiro M. Four cases presenting anaphylactic reactions due to topical application of Hibitane®. *Skin Res* 1983; **25**: 587–92

5 Harukuni I, Ishizawa Y, Nishikawa T, *et al.* Anaphylactic shock with ventricular fibrillation induced by chlorhexidine *Masui* 1992; **41**: 445–59

6 Nikaido S, Tanaka M, Yamoto M, Minami T, Akatsuka M, Mori H. Anaphylactoid shock caused by chlorhexidine gluconate. *Masui* 1998; **47**: 330–34

7 Association of Anaesthesists of Great Britain and Ireland Guidelines on Anaphylaxis (1995) at http://www.ncl.ac.uk/~nassoca/nanap.html

8 Edston E, van Hage-Hamsten M. Beta-Tryptase measurements post-mortem in anaphylactic deaths and in controls. *Forensic Sci Int* 1998; **93**: 135–42

9 Fisher MM and Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998; **80**: 26–9

10 Gueant J-L, Aimone-Gastin I, Namour F, Laroche D, Bellou A, Laxenaire M-C. Diagnosis and pathogenesis of the anaphylactic and anaphylactoid reactions to anaesthetics. *Clin Exp Allergy* 1998; **28**: 65–70

11 Moneret-Vautrin DA, Laxenaire MC, Moeller R. Anaphylaxis due to succinylcholine: immunoallergological study of thirteen cases. *Clin Allergy* 1981; **11**: 175–83

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Delayed diagnosis of cardiac tamponade following isolated blunt abdominal trauma

M. F. Dunsire*, J. Field and S. Valentine

Departments of Anaesthesia and Intensive Care, Fremantle Hospital, Alma Street Fremantle, WA 6160, Australia

**Corresponding author. Current address: Department of Anaesthesia, The Maritime Medway Hospital, Windmill Road, Gillingham ME7 5NY, UK*

Traumatic haemopericardium is an uncommon but life threatening condition. It is usually caused by penetrating cardiac injuries or cardiac rupture from blunt chest trauma. We report haemopericardium and cardiac tamponade in a young girl after blunt abdominal trauma. She presented with mild upper abdominal pain, tachycardia and hypotension having been kicked in the abdomen by a horse. No damage was found at laparotomy and she remained haemodynamically unstable. Further investigation found cardiac tamponade and haemopericardium. This was managed by insertion of a pericardial drain using transthoracic echocardiogram guidance, with later drainage in the operating theatre using guidance with a transoesophageal echocardiogram.

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Keywords: complications, cardiac tamponade; monitoring, transthoracic echocardiography; monitoring, transoesophageal echocardiography

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Acute cardiac tamponade is a condition with a considerable mortality unless diagnosis and appropriate treatment is prompt. We describe a case where diagnosis was significantly delayed and the patient had a laparotomy for presumed intra-abdominal haemorrhage. After the correct diagnosis was reached, the patient was managed by insertion of a pericardial drain and further monitoring and drainage guided by transoesophageal echocardiogram.

Case report

A 14-year-old girl presented at 17:30 to the emergency department of a peripheral hospital with a history of being kicked three times in the abdomen by a horse. She complained of epigastric and left upper quadrant pain. Initial examination revealed a tachycardia of 130 beats min^{-1}, arterial pressure of 95/65 mm Hg and mild epigastric tenderness. There was no open wound or evidence of chest injury. She declined analgesia. Intravenous access was obtained and fluid resuscitation commenced. Initial investigations revealed a haemoglobin (Hb) of 140 g litre^{-1}, normal plasma electrolytes and amylase. An electrocardiogram (ECG) and chest x-ray were not performed. The patient was admitted for observation. Two hours later her Hb was 125 g litre^{-1}. She remained hypotensive and tachycardic over the next 3 h with oliguria despite fluid administration. Because ultrasound and computed tomography studies were not available, laparotomy was done.

Anaesthesia was induced using fentanyl 100 μg and thiopentone 200 mg with suxamethonium 100 mg to achieve tracheal intubation. Anaesthesia was maintained with 0.8% isoflurane and 50% nitrous oxide in oxygen. Morphine 10 mg was given for intra- and postoperative analgesia. During the 2-h procedure, she was given 2 litres of Hartman's solution and 500 ml of Haemacell. Her systolic arterial pressure remained between 90 and 100 mm Hg throughout the procedure and her urine output at 20–30 ml h^{-1}. The surgical findings included free peritoneal fluid, an oedematous gall bladder and duodenum but no evidence of a ruptured viscus or intra peritoneal haemorrhage. Increased pressure in the inferior vena cava (IVC) and congested hepatic and portal veins were noted. After an hour in recovery, she was transferred to the ward where she remained hypotensive, tachycardic and oliguric despite another 6 litres of fluid (3 litres of crystalloid and 3 litres of

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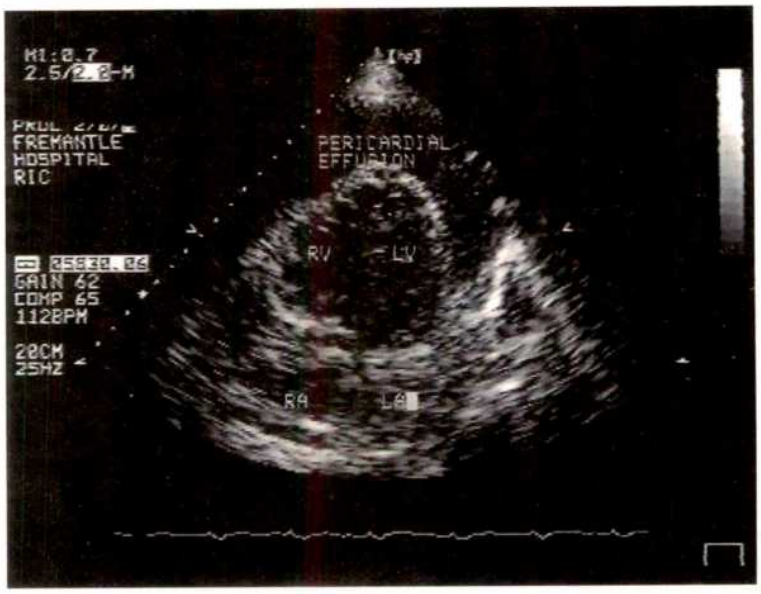

Fig 1 Transthoracic echocardiogram showing the four cardiac chambers and surrounding haemopericardium.

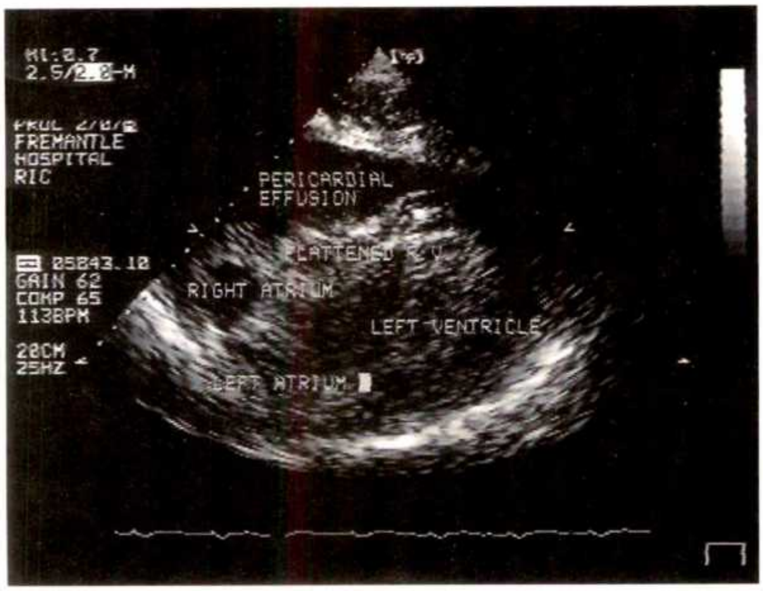

Fig 2 Transthoracic echocardiogram showing showing right ventricle (RV) being compressed by haemopericardium.

colloid). She was transferred to an intensive care unit (ICU) early the next morning.

On arrival in the ICU she was shocked, with a heart rate of 140 beats min^{-1} and arterial pressure of 70/30 mm Hg. Heart sounds were present and normal. Chest examination was normal. The abdomen was tender in keeping with recent laparotomy.

There was minimal serosanginous discharge from her abdominal drains. Fluid administration continued and a radial intra arterial cannula and right internal jugular central venous cannula were inserted. Infusions of norepinephrine and dopamine were commenced. Central venous pressure (CVP) was 22 mm Hg. An ECG showed sinus rhythm with normal size complexes, right ventricular dominance and peaked T waves. On chest x-ray, a right pleural effusion and normal cardiac outline were noted. Her Hb was 127 g litre^{-1} and arterial blood gas analysis showed pH 7.13, $P\text{CO}_2$ 59 mm Hg, $P\text{O}_2$ 103 mm Hg, bicarbonate 18 mmol litre^{-1} and base excess –11 mmol litre^{-1} ($F\text{I}_{\text{O}_2}$ 0.6). Plasma potassium was 6.5 mmol litre^{-1} and 50 ml of 50% dextrose and 15 units of insulin were given. In view of the hypotension and raised CVP the possibility of cardiac tamponade was considered. An urgent trans-thoracic echocardiogram (TTE) revealed a large pericardial effusion with cardiac tamponade (Figs 1, 2). A pericardial drain was placed using guidance by the TTE and 500 ml of fresh blood was aspirated cautiously with ease. There was very mild improvement in the haemodynamic condition but not complete drainage of the effusion. A cardiothoracic surgical opinion suggested a ruptured right ventricle as the likely diagnosis. The patient was urgently transferred to theatre with a view to sternotomy. In theatre, with a scrubbed surgical team in attendance, anaesthesia was induced using midazolam 4 mg, fentanyl 250 μg and rocuronium 50 mg to facilitate tracheal intubation. Anaesthesia was maintained with 0.5% isoflurane in oxygen/air. Phenylephrine 50 μg boluses were given in conjunction with the norepinephrine and dopamine infusions already being given. A trans-oesophageal echocardiogram showed a large pericardial effusion, tricuspid regurgitation and abnormal right ventricular wall motion consistent with myocardial contusion. Fresh blood (50 ml) was easily aspirated via the pericardial drain with no change in the size of the effusion and no improvement in cardiovascular state. Since blood was aspirated with ease, the effusion did not diminish in size and there was little improvement in haemodynamic state we considered that the drain could have inadvertently penetrated the ventricle. According to the TTE it was in the correct position but we could not see it with the TOE. To confirm pericardial placement of the pigtail catheter we injected 2 ml of Haemacell, which was seen on the TOE as echogenic bubbles within the pericardial sac. Using the TOE, a further 200 ml blood was aspirated from the pericardium until it was empty with marked improvement in the haemodynamic condition. Thirty minutes after complete drainage of the effusion no recurrence of the collection was seen on the TOE and we concluded that there was no ventricular rupture. Surgery was deferred and the patient was transferred to the ICU with the pericardial drain in place. A right intercostal catheter was placed and 850 ml blood drained. Serial TTE over the next 24 h showed no re-accumulation of fluid but there was significant abnormality of right ventricular wall motion consistent with contusion and mild tricuspid regurgitation. She was discharged from the ICU the next day. She made a good recovery over the next 2 weeks with discharge being delayed by an ileus.

Discussion

Cardiac injuries are the most commonly overlooked injuries in patients who die from trauma.[1] The true incidence of cardiac trauma is difficult to quantify although the incidence of blunt cardiac trauma requiring treatment may be as low as 2.6–4.5%.[2] Haemopericardium is usually caused by a penetrating cardiac injury or cardiac chamber rupture from blunt chest trauma. The literature abounds with such reports.[3–6] The case we describe is unusual on three counts. First, the site of the trauma was the upper abdomen and not the chest. Our patient was most specific that the blows were to her epigastrium alone although there can be no doubt that a significant degree of force must have been transmitted up across the diaphragm as well as in an antero-posterior direction across the abdomen. Secondly there was an unusually large amount of blood (700 ml) present in the pericardium without evidence of cardiac rupture. Thirdly the effusion was successfully drained with TOE guidance.

Symptoms of cardiac tamponade are usually rapid in onset but depend on the rate and volume of pericardial fluid accumulation. It is a diagnosis that needs a high index of suspicion, in one review four out of five cases were initially missed in 16 patients who presented to an emergency department with penetrating cardiac trauma,[7] and in 16 of 24 patients with atrial tears from blunt trauma the diagnosis was delayed by at least 1 h despite all 24 patients having an increased CVP or neck vein distension and hypotension.[8] In our case report the patient presented with a mechanism of injury suggesting intra abdominal injury and her initial clinical findings supported this. She had no 'classic' signs of tamponade, but Beck's triad (distended neck veins, muffled heart sounds and hypotension) is found in only 10% of trauma patients with tamponade.[9] It was unfortunate that a chest x-ray was not done early in management, because a haemothorax may have aroused suspicions, although she had no symptoms related to her chest at that time. Even with a haemothorax, the clinical features of cardiovascular instability and blunt abdominal trauma would make an intra peritoneal bleed the most likely diagnosis. However, if a chest x-ray done after a negative laparotomy, with the patient still hypotensive, showed a haemothorax then the possibility of serious chest injury would be considerable.

Induction of anaesthesia in these circumstances is fraught with difficulty. As fluid collects rapidly in the pericardial space pressure can increase quickly in the relatively indistensible parietal pericardium. Pressure changes are transmitted to the ventricle and this decreases the atrioventricular pressure gradient during diastole and impedes ventricular filling, causing a reduced end-diastolic volume and stroke volume.[10] Increased diastolic ventricular pressure will decrease the coronary perfusion pressure predisposing those with coronary artery disease to ischaemia, particularly if tachycardia is present. Compensatory mechanisms include increased sympathetic activity leading to increased heart rate and increased contractility, which help maintain cardiac output in the face of a reduced stroke volume and vasoconstriction to maintain central blood pressure and support the gradient for coronary flow.[10] The anaesthetic aims are therefore to maintain adequate filling pressures, adequate heart rate and maintain contractility. Anaesthesia for the laparotomy was induced with thiopentone, which is not the agent of choice as this can cause hypotension by venodilation and decreased venous return decreasing cardiac output with potentially disastrous consequences as was reported by Cyna *et al.*[11] Propofol is similarly contraindicated.

The patient remained relatively stable throughout her laparotomy with no haemodynamic deterioration. Laparotomy failed to provide a definitive cause for her cardiovascular instability although there were some clues. Haemoglobin concentration did not decrease and increased pressure on the IVC and congested hepatic and portal veins were noted. After surgery, the patient became increasingly shocked despite persistent administration of fluids and was extremely ill when she was transferred to intensive care.

Pigtail drainage catheter under echo guidance using local anaesthesia is the method of choice in the management of pericardial effusions and cardiac tamponade[12 13] and prevents the need for diagnostic needle pericardiocentesis which has a high false positive and false negative rate.[14] An unusually large amount of blood was aspirated (500 ml) with no diminution of flow, suggesting the possibility of right atrial or ventricular rupture. TOE probe placement is routine before all cardiac surgical procedures in our institution. This confirmed that the pigtail catheter was in the pericardial cavity and allowed the effusion to be drained under direct vision and to see if the effusion would reaccumulate. It also allowed the right ventricle, valves and interatrial septum to be seen more accurately than with the TTE. Because the effusion did not reaccumulate 30 min after drainage, we felt that cardiac rupture was not present and the patient could be managed conservatively without exploratory surgery. Without TOE, the patient would have undergone unnecessary surgery.

In summary pericardial tamponade is an uncommon but life threatening condition. It can mimic other conditions such as hypovolaemia particularly after trauma. A high index of suspicion must be retained if it is to be diagnosed and treated effectively.

References

1 Liedtke AJ, Demuth WEJ. Nonpenetrating cardiac injuries: A collective review. *Am Heart J* 1973; **86**: 687–97
2 Maenza RL, Seaberg D, D'Amico F. A meta-analysis of blunt cardiac trauma; ending myocardial confusion. *Am J Emerg Med* 1996; **14**: 237–41
3 Fulton JO, Nel L, De Groot K M, Von Oppell UO. Blunt cardiac rupture. *South African J Surg* 1998; **36**: 132–5
4 Symbas NP, Bongiorno PF, Synbas PN. Blunt cardiac rupture: The utility of emergency department ultrasound. *Ann Thoracic Surg* 1999; **67**: 1274–6
5 Petre R, Chilcott M. Blunt trauma to the heart and great vessels. *N Engl J Med* 1997; **336**: 626–32
6 Crawford R, Kasem H, Bleetman A. Traumatic pericardial tamponade: relearning old lessons. *J Accid Emerg Med* 1997; **14**: 252–7
7 Bleetman A, Kasem H, Crawford R. Review of emergency thoracotomy for chest injuries in patients attending a UK Accident and Emergency department. *Injury* 1996; **27**: 129–32
8 Patton AS, Guyton SW, Lawson DW, Shannon JM. Treatment of severe atrial injuries. *Am J Surg* 1981; **141**: 465–71
9 Demetriades D, van der Veen BW. Penetrating injuries of the heart: Experience over 2 years in South Africa. *J Trauma* 1983; **23**: 1034–41
10 Spodick DH. Pathophysiology of cardiac tamponade. *Chest* 1998; **113**: 1372–8
11 Cyna AM, Rodgers RC, McFarlane H. Hypotension due to unexpected cardiac tamponade. *Anaesthesia* 1990; **45**: 140–2
12 Salem K, Mulji A, Lonn E. Echocardiographically guided pericardiocentesis: The gold standard for the management of pericardial effusion and cardiac tamponade. *Can J Cardiol* 1999; **15**: 1251–5
13 Tsang TS, Oh JK, Seward JB. Diagnosis and management of cardiac tamponade in the era of echocardiography. *Clin Cardiol* 1999; **22**: 446–52
14 Baum VC. The patient with cardiac trauma. *J Cardiothoracic Vasc Anaesth* 2000; **14**: 71–81

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Ipsilateral thoraco-lumbar anaesthesia and paravertebral spread after low thoracic paravertebral injection

M. K. Karmakar*, **T. Gin and A. M.-H. Ho**

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong, People's Republic of China

**Corresponding author*

We report ipsilateral thoraco-lumbar anaesthesia and paravertebral spread of contrast after injection through a thoracic paravertebral catheter that was placed at the right T8–9 spinal level for pain management in a patient with multiple fractured ribs. We review the literature and describe the subendothoracic fascial communication between the thoracic paravertebral

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space and the retroperitoneal lumbar paravertebral region, which we propose, is the anatomical basis for ipsilateral thoraco-lumbar anaesthesia and paravertebral spread of contrast in our patient.

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Thoracic paravertebral injection of local anaesthetic produces ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes above and below the site of injection.[1] The origin of the psoas major muscle is described to completely seal off the thoracic paravertebral space below the level of the 12th thoracic vertebra[2] and caudal spread of a thoracic paravertebral injection below this level through the paravertebral space is thought to be unlikely.[2] Clinical ipsilateral thoraco-lumbar anaesthesia has occasionally been described,[1 3–5] challenging the concept of lumbar nerve sparing following thoracic paravertebral block.[2] To resolve this controversy, Saito *et al.* recently performed a cadaveric study and demonstrated ipsilateral spread of coloured dye from the thoracic paraverterbal space to the retroperitoneal lumbar paravertebral region.[6] Dye was seen to spread in the endothoracic fascia of the thorax and extend into the abdomen through the medial and lateral arcuate ligaments to involve the fascia transversalis and the lumbar spinal nerves.[6] However, the fascial communications between the thoracic paravertebral space and the retroperitoneal lumbar paravertebral region were not discussed in this report[6] and the authors state that 'the actual fluid communications between the endothoracic and transversalis fascias is not well-known'.[6] Thus the fascial communication between the thoracic paravertebral space and the retroperitoneal space still remains unexplained. In this report we describe ipsilateral thoraco-lumbar anaesthesia and paravertebral spread of contrast in vivo and review the fascial communications between the lower thoracic paravertebral space and the retroperitoneal space to account for this spread.

Case report

A 63-year-old previously healthy man, weighing 60 kg was referred to our pain team for management of right-sided fractured ribs, which had compromised his ability to breathe deeply and cough effectively. Pain was rated as severe by the patient with a visual analogue score (VAS: 0 – no pain and 100 – worst imaginable pain) of 80 at rest and 100 on coughing. Oxygen saturation was 96% with Pa_{O_2} 7.8 kPa and Pa_{CO_2} 4.4 kPa breathing room air. A chest radiograph demonstrated fractured right 8–10th ribs with no pneumothorax or haemothorax. After informed consent, a right-sided thoracic paravertebral block was performed at the level of T7–8 with the patient in the sitting position using a 16-gauge Tuohy needle (Minipack, Portex, UK) according to the technique described by Eason and Wyatt,[7] and 3 cm of the catheter was inserted into the paravertebral space. With the catheter safely secured to the back, the patient was returned to the supine position. After negative aspiration of the catheter for blood and CSF, 18 ml of 0.5% bupivacaine with 1:200 000 epinephrine was administered in small aliquots over a 3-min period. The patient soon became pain free. Thirty minutes following the paravertebral injection, the VAS for pain was 0 at rest and 20 on coughing, and ipsilateral anaesthesia to temperature (cold) was elicited from the T7–T10 dermatomes with no contralateral extension. A continuous infusion of bupivacaine 0.25% was commenced at 7 ml h^{-1} and regular oral diclofenac 75 mg twice daily was also prescribed. The patient remained

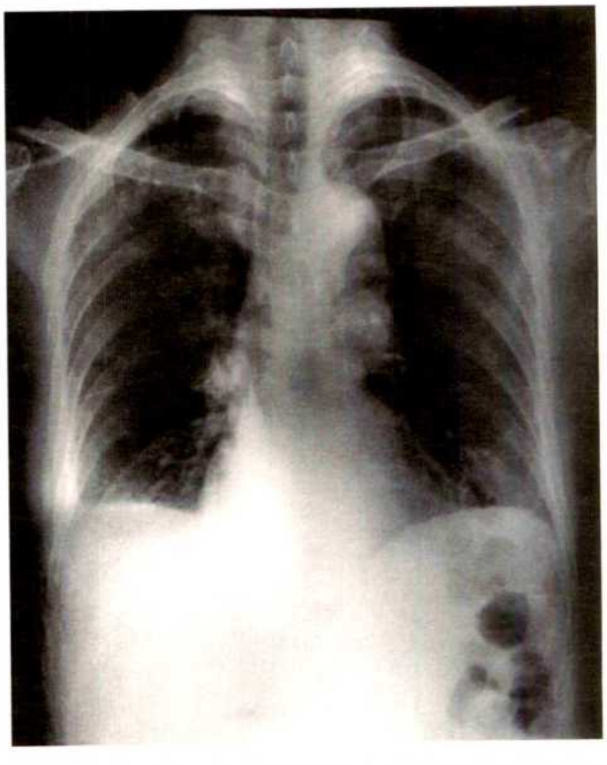

Fig 1 Chest x-ray (anteroposterior view) after injection of contrast through the paravertebral catheter. Note ipsilateral thoraco-lumbar paravertebral spread from T10 to L2.

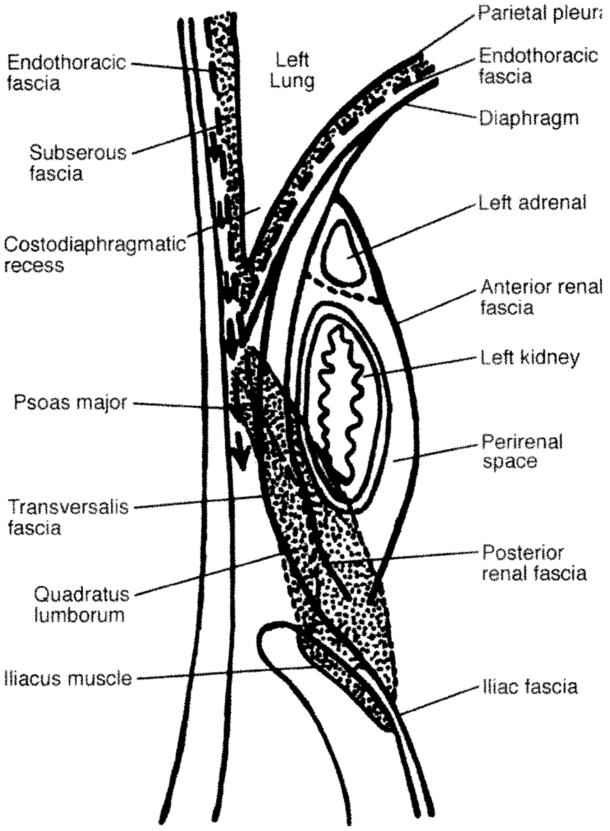

Fig 2 Saggital section showing the fascial relations of the lower thoracic paravertebral space and the retroperitoneal space.

comfortable, was able to breathe deeply, complied with chest physiotherapy and was soon mobilized. On the second day after the thoracic paravertebral catheter placement, it was noted that the patient was having increasing pain (VAS: 30 at rest and 70 on coughing). On clinical examination there was no demonstrable cutaneous anaesthesia over the chest or abdomen and on inspection of the catheter insertion site it was apparent that the catheter had dislodged out of the thoracic paravertebral space.

After discussion with the patient, he requested to have the thoracic paravertebral catheter resited. Using the same technique the right thoracic paravertebral space was accessed one interspace lower at the T8–9 level and 3 cm of catheter was inserted into the thoracic paravertebral space. The catheter was tunneled subcutaneously and safely secured to the back. A total of 10 ml of 0.5% bupivacaine with 1:200 000 epinephrine was injected via the catheter over a 2-min period with the patient in the supine position. The patient once again became pain free. Thirty minutes following the injection, the VAS was 0 at rest and 20 on coughing and ipsilateral cutaneous anaesthesia to temperature (cold) was elicited from T7–L3 dermatomes. There were no significant haemodynamic changes or evidence of motor blockade in the distribution of the lumbar spinal nerves bilaterally as judged by normal hip flexion, knee extension and hip adduction.

To confirm the position of the catheter and demonstrate the spread of the paravertebral injection 10 ml of Iopamiro-300 (Iopamidol-300 mg ml^{-1}, Bracco s.p.a., Milano, Italia)

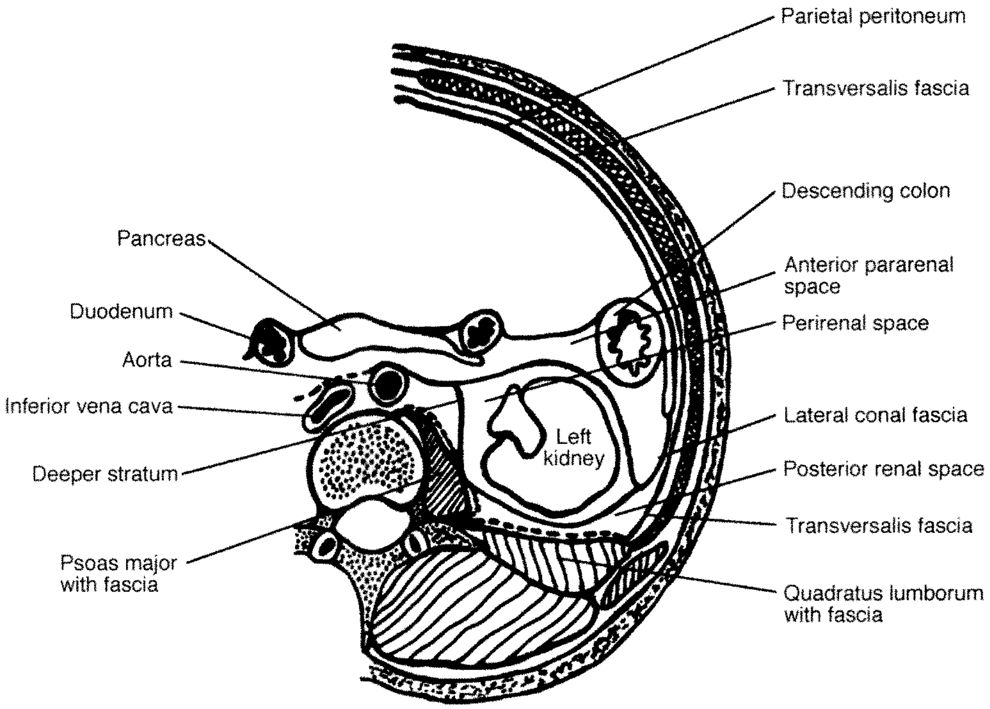

Fig 3 Anatomical relations of the fascia covering the psoas major, quadratus lumborum and fascia transversalis to the retroperitoneal space.

was injected via the indwelling paravertebral catheter distal to the bacterial filter. Immediately following this injection an anteroposterior chest x-ray was taken (Fig. 1). Ipsilateral paravertebral spread of contrast from the ninth thoracic to the second lumbar segment below the diaphragm was noted on the chest x-ray (Fig. 1).

Discussion

Thoracic paravertebral injection of local anesthetic produces ipsilateral somatic and sympathetic nerve blockade in multiple thoracic dermatomes above and below the site of injection.[1] This results from spread to the contiguous thoracic paravertebral space,[8–10] the intercostal space laterally[8–10] and the epidural space medially.[8 9 11] The thoracic paravertebral injection in our patient also produced multidermatomal ipsilateral thoracic anaesthesia, which was effective in relieving pain caused by the multiple fractured ribs. However after the second paravertebral injection we observed ipsilateral thoraco-lumbar anaesthesia extending from T7 to L3 dermatomes with no motor involvement of the lumbar spinal nerves. The post-contrast chest x-ray also demonstrates ipsilateral thoraco-lumbar (T9–L2) paravertebral spread of contrast (Fig. 1).

There is controversy whether low thoracic paravertebral block can extend into the lumbar region. Lönnqvist and Hildingsson examined the caudal limit of the thoracic paravertebral space in eviscerated cadavers by approaching the thoracic paravertebral space internally from the thoracic cavity.[2] Based on observations made after probing and dye injection, they concluded that the origin of the psoas major muscle completely sealed off the thoracic paravertebral space below the level of the 12th thoracic vertebra, and proposed that spread of a thoracic paravertebral block below this level through the paravertebral space was unlikely.[2] However ipsilateral thoraco-lumbar anaesthesia,[1 3–5] radiological spread of contrast below the diaphragm[9] and thoraco-lumbar spread of coloured dye in cadavers[6] has been described,[1 4–6 9] challenging the concept of lumbar nerve sparing following thoracic paravertebral block.[2]

The incidence of ipsilateral thoraco-lumbar anaesthesia after thoracic paravertebral block is not known but published data suggest that it is more common after low thoracic paravertebral injections.[1 3–5] Richardson *et al.* report ipsilateral L1 spinal nerve involvement in three of the ten patient studied after paravertebral injection of 1.5 mg kg^{-1} bupivacaine 0.5% at T6 and T10 level respectively.[3] Cheema *et al.* performed paravertebral injections at a mean level of T9–10 (range T7–8 to T10–11) and report mean ipsilateral anaesthesia of five dermatomes (range 1–8), with upper and lower limits of T6 and L3, after 15 ml of bupivacaine 0.5%.[1] Saito *et al.* report 'broad unilateral anaesthesia' extending from the left T4 to L3 after injection of local anesthetic through an epidural catheter, which was inadvertently inserted in the left T11 paravertebral space.[5] More recently, Saito *et al.*, in a cadaveric study, demonstrated ipsilateral retroperitoneal lumbar paravertebral spread of crimson dye along the endothoracic fascia and fascia transversalis through the medial and lateral arcuate ligament, after thoracic paravertebral injection at T11.[6] The dye stained the ipsilateral subcostal, iliohypogastric, ilioinguinal, genitofemoral and lateral femoral cutaneous nerve in all 12 cadavers studied, and in two cases the dye also reached the femoral nerve.[6] On average, spread extended from the 6th intercostal nerve to the lateral femoral cutaneous nerve (T6–L2).[6] All of these reports of ipsilateral thoraco-lumbar anaesthesia[1 3–5] and paravertebral spread[6 9] *in vivo*[1 3–5 9] and in cadavers[6] suggests that there is a fascial plane of communication between the ipsilateral thoracic paravertebral space and the retroperitoneal space. Review of the literature shows that such an anatomical plane of communication exists which may account for ipsilateral thoraco-lumbar anaesthesia.

The endothoracic fascia, also referred to as the 'internal thoracic fascia', is a fibroelastic structure that forms the deep fascia of the thorax and lines the internal surface of the intercostal muscle, the intervening ribs, and the diaphragm.[12] At the diaphragm, the endothoracic fascia is very thin,[6 13] being thinnest at the upper surface and thickest at its edges.[6] Inferiorly the endothoracic fascia is continuous with the fascia transversalis (Fig. 2),[6 12 13] which is the deep fascia of the abdomen. This continuity occurs dorsal to the diaphragm through the medial and lateral arcuate ligament (lumbo-costal arch) and the aortic hiatus.[6 12 13] The fascia transversalis blends medially with the anterior layer of the quadratus lumborum fascia and the psoas fascia (psoas sheath) (Fig. 3).[14] The subcostal (T12), iliohypogastric (L1) and ilioinguinal (L1) nerves course anterior to and in contact with the quadratus lumborum,[15] while the genitofemoral nerve (L1, L2) descends on the ventral surface of the psoas major muscle and the lateral femoral cutaneous nerve (L2, L3) crosses the lateral border of the psoas muscle at the level of the inferior margin of L4 vertebra[15] in this fascial plane.

The fascia overlying the upper end of the psoas major muscle (psoas fascia) is thickened to form the medial arcuate ligament, which is attached medially to the body of L2 and laterally to the transverse process of L1.[14] The psoas major muscle courses under this fascial arch, also referred to as the 'open end of the psoas sheath',[14] to enter the posterior mediastinum and lie in contact with the lower thoracic vertebra and pleura.[14] It is through this fascial arch that tuberculous suppuration of the lower thoracic spine is thought to enter the psoas sheath and present as an abscess in the retroperitoneum or groin.[14] This may also be the route by which the genito-femoral nerve, which lies on the ventral surface of the psoas major muscle,[15] is involved.[6] Lönnqvist and Hildingsson, in their cadaver study, also observed passage of a guide wire or dye below the level of T12 in the fascial plane above the psoas muscle on two occasions, which the authors attributed to over-vigorous probing or injection,[2] but may also be explained by the above mechanism.

Based on the fascial anatomy described, an injection in the lower thoracic paravertebral space posterior to the endothoracic fascia can spread caudally via the medial and lateral arcuate ligament to the retroperitoneal space in the abdomen.[4] Since this results in spread anterior to the surface of the quadratus lumborum and psoas major muscle, the subcostal, iliohypogastric, ilioinguinal, genitofemoral and the lateral femoral cutaneous nerve may be involved.[6] This is the anatomical basis of the technique of 'extended unilateral anaesthesia'[4] and may also be the mechanism involved in our patient.

In summary, this case report demonstrates that ipsilateral thoraco-lumbar anaesthesia and paravertebral spread can occur after low thoracic paravertebral injection. Based on current evidence and anatomical knowledge the mechanism for this observation is an extended subendothoracic fascial spread from the thoracic paravertebral space to the retroperitoneal space in relation to the anterior surface of the psoas major and quadratus lumborum muscle where it affects the lumbar spinal nerves. This may have clinical application in the management of acute and chronic pain of unilateral thoraco-lumbar origin.

References

1 Cheema SP, Ilsley D, Richardson J, Sabanathan S. A thermographic study of paravertebral analgesia. *Anaesthesia* 1995; **50**: 118–21
2 Lönnqvist PA, Hildingsson U. The caudal boundary of the thoracic paravertebral space. A study in human cadavers. *Anaesthesia* 1992; **47**: 1051–2
3 Richardson J, Jones J, Atkinson R. The effect of thoracic paravertebral blockade on intercostal somatosensory evoked potentials. *Anesth Analg* 1998; **87**: 373–6
4 Saito T, Gallagher ET, Cutler S, *et al.* Extended unilateral anesthesia. New technique or paravertebral anesthesia? *Reg Anesth* 1996; **21**: 304–7
5 Saito T, Gallagher ET, Yamada K, Tanuma K, Ogawa R. Broad unilateral analgesia. *Reg Anesth* 1994; **19**: 360–1
6 Saito T, Den S, Tanuma K, Tanuma Y, Carney E, Carlsson C. Anatomical bases for paravertebral anesthetic block: fluid communication between the thoracic and lumbar paravertebral regions. *Surg Radiol Anat* 1999; **21**: 359–63
7 Eason MJ, Wyatt R. Paravertebral thoracic block—a reappraisal. *Anaesthesia* 1979; **34**: 638–42
8 Conacher ID. Resin injection of thoracic paravertebral spaces. *Br J Anaesth* 1988; **61**: 657–61
9 Conacher ID, Kokri M. Postoperative paravertebral blocks for thoracic surgery. A radiological appraisal. *Br J Anaesth* 1987; **59**: 155–61
10 Karmakar MK, Kwok WH, Kew J. Thoracic paravertebral block: radiological evidence of contralateral spread anterior to the vertebral bodies. *Br J Anaesth* 2000; **84**: 263–5
11 Purcell-Jones G, Pither CE, Justins DM. Paravertebral somatic nerve block: a clinical, radiographic, and computed tomographic study in chronic pain patients. *Anesth Analg* 1989; **68**: 32–9
12 Karmakar MK, Chung DC. Variability of a thoracic paravertebral block. Are we ignoring the endothoracic fascia? *Reg Anesth Pain Med* 2000; **25**: 325–7
13 Dugan DJ, Samson PC. Surgical significance of the endothoracic fascia. The anatomic basis for empyemectomy and other extrapleural technics. *Am J Surg* 1975; **130**: 151–8
14 Donovan PJ, Zerhouni EA, Siegelman SS. CT of the psoas compartment of the retroperitoneum. *Semin Roentgenol* 1981; **16**: 241–50
15 Farny J, Drolet P, Girard M. Anatomy of the posterior approach to the lumbar plexus block. *Can J Anaesth* 1994; **41**: 480–5

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Another feature of TURP syndrome: hyperglycaemia and lactic acidosis caused by massive absorption of sorbitol

C. A. Trépanier[1]*, M. R. Lessard[1], J. Brochu[1] and G. Turcotte[2]

[1]Department of Anesthesia and [2]Department of Biochemistry, Centre hospitalier affilié universitaire de Québec (Hôpital Enfant-Jésus), Laval University, 1401, 18e Rue, Québec, PQ, G1J 1Z4 Canada

**Corresponding author*

Endoscopic transurethral resection of the prostate (TURP) can be complicated by absorption of a large volume of irrigation fluid. The clinical features of this complication are referred as the TURP syndrome. We report a case where hyperglycaemia and lactic acidosis complicated the TURP syndrome caused by the massive absorption (approximately 15 litres) of a sorbitol–mannitol irrigation solution. The proposed mechanism is a type B lactic acidosis related to the metabolism of sorbitol.

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The transurethral resection of the prostate (TURP) syndrome is caused by the passage of irrigating fluid into the vascular space. Depending on the nature and the amount of fluid absorbed, the TURP syndrome may affect many systems mainly through acute changes in vascular volume and plasma solute concentrations.[1 2] Sorbitol–mannitol solutions are widely used for TURP mostly because, unlike glycine, these two solutes are considered to be devoid of toxicity.[3] We report a case of massive absorption of a sorbitol–mannitol irrigating solution which was complicated by hyperglycaemia and type B lactic acidosis. The metabolism of sorbitol which led to this complication is also reviewed.

Case report

A 71-yr-old, 58 kg man with benign hyperplasia of the prostate was scheduled for TURP under regional anaesthesia. Apart from a history of transient cerebral ischaemic attacks, his medical history was unremarkable. His usual medication was aspirin and doxazosine. No premedication was given and spinal anaesthesia was achieved with 1.4 ml of 0.75% hyperbaric bupivacaine injected through a 22-gauge Whitacre needle at the L4–L5 interspace. A T-7 sensory block height was obtained followed by a slight decrease of systolic arterial pressure from 130 to 115 mm Hg which was judged to require no treatment. During the procedure, normal saline was infused in a peripheral vein, no sedation was given and the patient received supplemental oxygen by nasal prongs.

The prostate was resected using a Storz Iglesias resectoscope through a modified cystoscope continuously irrigated with a solution of 2.7% sorbitol and 0.54% mannitol (Abbott Laboratories, Montreal, Canada). The irrigation fluid bags were hung 60 cm above the operating table. Surgery proceeded without any problem for 50 min, the patient was calm and responsive, and his blood pressure, heart rate and oxygen saturation were normal. Then the patient complained of shortness of breath and his oxygen saturation decreased to 91%. At that point, a total of 24 litres of irrigation fluid had been used, 55 g of prostate tissue had been resected, and the decision was made to terminate surgery. During that time the patient became more dyspnaeic and his respiratory rate increased to 30 bpm. One hundred per cent oxygen was given by face mask and the oxygen saturation returned to 98% but the patient became restless. Blood was sampled for measurement of electrolyte concentrations. The patient was transferred to the recovery room where he was allowed to stay in the sitting position and his respiration was supported by non-invasive positive pressure ventilation. After that, he was more co-operative although he remained slightly drowsy. Throughout this period, sinus tachycardia was present but the patient's blood pressure remained within normal limits. Obvious signs of pulmonary oedema were present on the chest x-ray but, except for sinus tachycardia, no abnormality was present on the ECG. Furosemide 40 mg i.v. was given and an infusion of nitroglycerine was started. An arterial cannula was inserted and serial blood samples were collected for measurement of blood glucose, serum sodium and osmolality, pH, $P\text{CO}_2$, $P\text{O}_2$, bicarbonate and arterial blood lactate (Table 1). At the end of surgery, serum concentration of sodium was 97 mmol litre^{-1} and increased progressively in the recovery room. Blood glucose was normal at the end of surgery but increased steadily during

Table 1 Evolution of postoperative blood acid–base and chemistry values. *O_2 saturation at time 00:00 was measured by pulse oximetry. Subsequent O_2 saturations were measured by hemoximetry

Parameter	**Time after end of surgery (h:min)**									
	00:00	**01:00**	**01:30**	**02:00**	**02:30**	**03:00**	**03:30**	**04:00**	**04:30**	**05:00**
Glucose (mmol litre^{-1})	5.3	9	13.4	16.6	17.9	18.1	16.5	14.8	12.8	11
Na (mmol litre^{-1})	98	104	108	110	111	112	115	115	118	119
$P\text{O}_2$ (mm Hg)		108	62	59	117	129	118	202	62	99
O_2 saturation* (%)	98	97	91	91	97	96	96	98	91	96
pH		7.31	7.29	7.30	7.32	7.32	7.34	7.35	7.32	7.37
Bicarbonates (mmol litre^{-1})		18.4	18.4	17.4	18	19.4	19.5	20.2	19.4	20.4
Lactate (mmol litre^{-1})		4.3	5.3	6.8	5.9	5.5	5.7	5.9	6.5	6.4
Osmolality (mmol kg^{-1})					286				280	

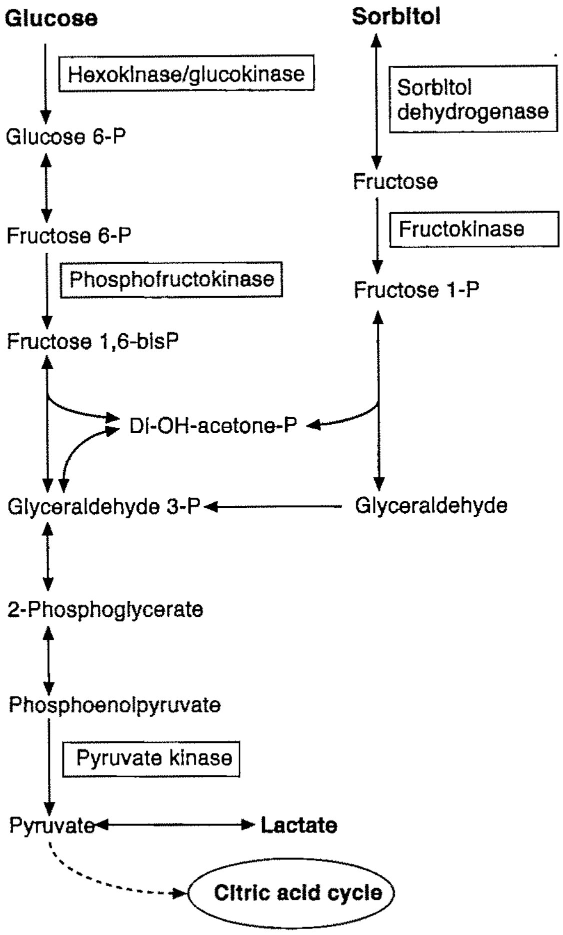

Fig 1 Pathways of glycolysis (Embden-Meyerhof pathway) and fructolysis along with major regulatory steps in the metabolism of glucose and sorbitol towards lactate production (see text). For simplicity and clarity purposes, four regulatory enzymes of glucose synthesis from lactate (gluconeogenesis) have been omitted from the figure.

the first hours after surgery. This was treated with i.v. human insulin and progressively improved. Blood-gas analysis done shortly after the end of surgery showed metabolic acidosis with elevated blood lactate. In the first few hours the acidosis increased, then slowly corrected without specific therapy but arterial lactate remained elevated for the whole recovery room stay. The pulmonary oedema improved rapidly and both nitroglycerine and ventilatory assistance were easily weaned in less than 3 h. Apart from postoperative nausea and vomiting which was treated with droperidol and ondansetron, the patient improved rapidly. He made an uneventful recovery and was discharged home 2 days later.

Discussion

Sorbitol and mannitol are electrically non-conducting but osmotically active solutes that are added to irrigation fluids to decrease the risk of massive intravascular haemolysis.[1 2] Because these solutions are devoid of the risk of hyperammonaemia and hyperglycinaemic encephalopathy associated with glycine solutions, they are widely used in urologic endoscopic surgery.[3] With these solutions, the clinical signs and symptoms of the TURP syndrome are believed to be caused by the massive absorption of fluid and the resulting hyponatraemia and hypo-osmolality and not by any toxicity of sorbitol or mannitol.[1 3] To the best of our knowledge, this is the first report of hyperglycaemia and lactic acidosis associated with absorption of sorbitol–mannitol irrigation solution.

Mannitol is a sugar alcohol derived from mannose that is not metabolized and is rapidly excreted by glomerular filtration in the kidney.[4] Sorbitol is a natural C6-sugar alcohol found in many fruits. It is metabolized to fructose by sorbitol dehydrogenase in the liver and to a lesser extent in the kidney (Fig 1).[4] One might anticipate that high doses of sorbitol could induce toxic effects similar to fructose toxicity such as lactic acidosis, hyperuricaemia and hyperglycaemia. Lactic acidosis following fructose infusions may be caused by a combination of several mechanisms. First, in the presence of both fructose and glucose, the formation of fructose 1-phosphate is favoured by the higher fructokinase activity compared with the lesser capacity of hexokinase plus glucokinase to phosphorylate glucose. Second, the fructolysis of fructose 1-phosphate by aldolase bypasses phosphofructokinase, the first regulatory enzyme along the glycolysis pathway towards pyruvate and lactate formation. Third, fructose 1-phosphate and fructose 1,6-biphosphate stimulate pyruvate kinase, the second regulatory step of glycolysis.[4] The hyperglycaemia observed in this case may be explained by the much higher activity of fructokinase that favours the formation of fructose 1-phosphate over glucose 6-phosphate, thus restraining glucose metabolism while favouring fructose metabolism towards pyruvate and lactate and providing substrate for gluconeogenesis.[4 5] Indeed, in the isolated liver perfused with fructose, about 50–75% of the fructose is retrieved as glucose and the rest as lactate and pyruvate.[6 7]

Causes of lactic acidosis are classified as type A where poor tissue oxygenation is present and type B where tissue oxygenation is preserved.[8] In such a case of TURP syndrome presenting with pulmonary oedema, metabolic acidosis when present is usually attributed to type A lactic acidosis caused by hypoxaemia and tissue hypoperfusion. Our patient never presented hypotension or significant oxygen desaturation, thus making a type A aetiology unlikely. Sorbitol and fructose are among the numerous causes of type B lactic acidosis. For instance, fructose was abandoned for parenteral nutrition several years ago because of associated metabolic disturbances similar to those encountered in this case.[9 10] Furthermore, Buijs and van Zuilen have reported a time course of blood glucose, lactate and acid–base disturbances remarkably similar to this case in a patient who received 250 ml of 30% sorbitol (7.5 g) for brain volume reduction.[11] In the present case, based upon the serum concentration of sodium at the end of surgery, the calculated volume of irrigation solution absorbed was approximately 15 litres and the amount of sorbitol absorbed can be estimated at around 40 g, many times the amount previously reported to cause type B lactic acidosis.[11] Finally, a milder case of lactic acidosis during TURP has been recently reported with a low volume absorption (500 ml) of a sorbitol–mannitol solution and might also be explained by the same mechanism.[12]

The clinical presentation of lactic acidosis varies greatly. In type A, the signs and symptoms of the underlying problem dominate the clinical picture. However patients with type B may present with a variety of symptoms such as hyperventilation, malaise, weakness, nausea, vomiting, abdominal pain and progressive mental clouding.[8] These symptoms are frequently encountered in the TURP syndrome but are usually believed to be caused by hypervolaemia and hyponatraemia. Many of these symptoms were present in this case and were at least in part caused by lactic acidosis, especially in the recovery phase when hypervolaemia and hyponatraemia were improving while blood lactate was still elevated. It should be noted that both type A and B lactic acidosis may occur simultaneously. Hypoxaemia and hypoperfusion are often present in the TURP syndrome and will prevent the entry of pyruvate into the citric acid cycle, thus further increasing production of lactate.

In summary, we report a case where hyperglycaemia and lactic acidosis complicated the TURP syndrome caused by the massive absorption of a sorbitol–mannitol irrigating solution. We suggest that blood glucose and arterial lactate concentration should be measured when an important absorption of sorbitol–mannitol is suspected and that type B lactic acidosis is a possible cause of metabolic acidosis in such cases.

References

1 Gravenstein D. Transurethral resection of the prostate (TURP) syndrome: a review of the pathophysiology and management. *Anesth Analg* 1997; **84**: 438–46

2 Hahn RG. Irrigating fluids in endoscopic surgery. *Br J Urol* 1997; **79**: 669–80

3 Dawkins GP, Miller RA. Sorbitol-mannitol solution for urological electrosurgical resection, a safer fluid than glycine 1.5%. *Eur Urol* 1999; **36**: 99–102

4 Gitzelmann R, Steinmann B, Van den Berghe G. Disorders of fructose metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 7th Edn. New York: McGraw-Hill Inc, 1995; 905–34

5 Harris RA. Carbohydrate metabolism I: Major metabolic pathways and their control. In: Devlin TM, ed. *Textbook of Biochemistry with Clinical Correlations*, 4th Edn. New York: Wiley-Liss Inc, 1997; 267–333

6 Woods HF, Eggleston LV, Krebs HA. The cause of hepatic accumulation of fructose-1-phosphate on fructose loading. *Biochem J* 1970; **119**: 501–10

7 Wolfe BM, Ahuja SP, Marliss EB. Effects of intravenously administered fructose and glucose on splanchnic amino acid and carbohydrate metabolism in hypertriglyceridemic men. *J Clin Invest* 1975; **56**: 970–7

8 Cohen RD, Iles RA. Lactic acidosis: diagnosis and treatment. *Clin Endocrinol Metab* 1980; **9**: 513–27

9 Sahebjami H, Scalettar R. Effects of fructose infusion on lactate and uric acid metabolism. *Lancet* 1971; **1**: 366–9

10 Woods HF, Alberti KG. Dangers of intravenous fructose. *Lancet* 1972; **2**: 1354–7

11 Buijs EJ, van Zuilen HJ. Metabolic consequences of a sorbitol overdose during neurosurgery. *J Neurosurg Anesthesiol* 1997; **9**: 17–20

12 Scheingraber S, Heitmann L, Weber W, Finsterer U. Are there acid base changes during transurethral resection of the prostate (TURP)? *Anest Analg* 2000; **90**: 946–50

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Correspondence

Incidence of awareness in total intravenous anaesthesia

Editor—In a previous study with i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade, we reported two patients among 1000 who had explicit recall of intraoperative events.[1] Using the same anaesthetic method in 45 female patients, Russell and Wang recently reported no case of explicit recall.[2] However, by using the isolated forearm technique, seven of their 45 patients responded to command on a total of 12 occasions.[2] It seems disturbing that patients have significant cognitive function during general anaesthesia, yet are amnesic. However, for the following reasons, the methods used in these two studies may not have been comparable.

(i) The patients were interviewed by Russell and Wang within 2h of anaesthesia, while Nordström followed the patients up to approximately 1 week after surgery, and one of the two patients identified actually had no explicit recall until the interview on day 8. It has been demonstrated that an early interview may fail to recognize up to 50% of patients who will develop explicit recall.[3] Thus, by using a longer follow-up period, it is possible that Russell and Wang would have been able to identify explicit recall among their patients.

(ii) Different premedication was used in the two studies. It seems probable that the sedative and analgesic effects of the premedication used by Russell and Wang, were, on average, less intense.

(iii) The loading dose of alfentanil used by Russell and Wang was approximately 10 μg kg^{-1} while Nordström used between 25 and 50 μg·kg^{-1} titrated according to individual response before propofol was started. Simulations (Rugloop, kinetics according to Shafer) indicate that Nordström used at least a 60% higher target site concentration of alfentanil during surgery.

(iv) Russell and Wang mixed alfentanil and propofol in the same syringe. They seem to have aimed to reach an infusion rate of propofol of only 4 mg kg^{-1}h^{-1} in patients between 26 and 57 years old. Nordström used separate infusions of alfentanil and propofol, and the lowest recommended infusion rate of propofol was 6 mg kg^{-1}h^{-1} (modified according to lean body mass and age). An infusion rate as low as 4 mg kg^{-1}h^{-1} was only allowed by Nordström in elderly patients with severe hypotension despite adequate volume loading (patients up to 89 years old were included).

(v) Finally, noxious surgical stimulation was abolished by epidural analgesia in Russell's study, and low effect site concentrations of alfentanil and propofol were evident when patients were responsive. It should also be questioned if up to 20 min of ischaemia, distal to the tourniquet used to isolate the forearm from the muscle relaxant, actually contributed to the arousal of these patients.

For these reasons, and the fact that only two of the 12 responses to command found by Russell and Wang occurred at an infusion rate of propofol 6 mg kg^{-1}h^{-1} or more (6 and 7 mg kg^{-1}h^{-1} respectively), it is by no means certain that an incidence of responsiveness of 17.5% actually corresponds to 0.2% explicit recall. However, the major finding by Russell and Wang, concerning lack of implicit memory in non-responsive patients, is not altered by this comment, and they deserve credit for their efforts to ensure that patients are actually anaesthetised, not only amnesic.

Rolf Sandin
Kalmar, Sweden

1 Nordström O, Engström AM, Persson S, Sandin R. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. *Acta Anaesthesiol Scand* 1997; **4**: 978–84
2 Russell IF, Wang M. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. *Br J Anaesth* 2001; **86**: 196–202
3 Sandin RH, Enlund G, Samuelsson P, Lannmarken C. Awareness during anaesthesia: A prospective case study. *Lancet* 2000; **355**: 707–11.

Editor—Thank you for the opportunity to respond to the letter from Dr Sandin. Owing to an oversight (my fault) there is a reference missing from our study.[1] The actual technique on which our paper was based was that described by Sandin and Nordström in 1993.[2] In that study, the lowest doses of propofol administered to patients under 60 years old who also had an epidural was 3.6 mg kg^{-1}h^{-1}.[2] When compared to this study,[2] our study[1] used approximately 30% more propofol but less alfentanil. Since all patients in our study had epidurals, the arousal effects of surgery would have been minimal. That first retrospective study, conducted in the early learning phase of the introduction of TIVA to their institution, identified a 0.2% incidence of awareness with recall.[2] This 0.2% incidence of awareness with recall is the same as in the paper we misquoted,[3] and in the most recent paper from that institution.[4] It would thus seem that even with very careful follow up, a very reasonable estimate of the incidence of awareness with recall in a TIVA technique based on propofol and alfentanil is 0.2%.

The results of our study[1] show that the incidence of postoperative recall bears no relationship to the incidence of intraoperative awareness. Dr Sandin is correct in drawing attention to the differences in technique between the two studies[1,3] and in emphazing the importance of ensuring that patients are actually anaesthetized, not merely paralysed and amnesic.

Ian F. Russell
M. Wang
Kingston-upon-Hull
UK

1 Russell IF, Wang M. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. *Br J Anaesth* 2001; **86**: 196–202
2 Sandin R, Nordström O. Awareness during total intravenous anaesthesia. *Br J Anaesth* 1993; **71**: 782–7
3 Nordström O, Engström AM, Persson S, Sandin R. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular block. *Acta Anaesthesiol Scan* 1997; **41**: 978–84
4 Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: A prospective case study. *Lancet* 2000; **355**: 707–11.

Use of pre-emptive vasopressors for spinal anaesthesia-induced hypotension during Caesarean section

Editor—We read with interest the article by Buggy and colleagues on the use of pre-emptive vasopressors for spinal anaesthesia-induced hypotension during Caesarean section. Our first comment regarding this paper concerns the population studied, which appears to be heterogeneous. We also find it noteworthy that the median parity in the control group is 2, as it is 1 in all other groups. Second, the power analysis performed prior to the study

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used an incidence of 80% for hypotension as its basis. This is, as the authors state, at the upper end of the reported spectrum and in fact not supported in their own study. One has therefore to question the validity of their power analysis.

Apart from these theoretical considerations, it is interesting that there is no significant reduction in the incidence of ephedrine requirement between the control and treatment groups suggesting that the vasopressors in the treatment groups were administered in response to the side-effects of nausea, vomiting and dizziness. Only for the P4 group (prophylactic phenylephrine 4 mg i.m.) is there a significant reduction in the incidence of hypotension. Furthermore, there is no difference in the neonatal outcome as measured by Apgar scores. Although the authors state that the use of phenylephrine 4 mg i.m. and ephedrine 45 mg i.m. reduced the dose of rescue i.v. ephedrine, the overall amount of vasopressor administered is markedly increased through this practice. From the parturients' point of view, all the i.m. injection of a vasopressor has achieved is a reduction in the incidence of low values for the cardiovascular variables. No benefit has been gained in terms of terms of reducing the distressing side-effects of spinal anaesthesia, (i.e. nausea, vomiting and dizziness) nor has neonatal outcome been improved. Thus routine use of i.m. vasopressors in obstetric anaesthesia appears unwarranted.

Bernhard H. Heidemann
Vicki A. Clark
Simpson Memorial Maternity Pavillion
Edinburgh
UK

1 Ayorinde BT, Buczkowski P, Brown J, Shah J, Buggy DJ. Evaluation of pre-emptive intramuscular phenylephrine and ephedrine for reduction of spinal anaesthesia-induced hypotension during Caesarean section. *Br J Anaesth* 2001; **86**: 372–6

Editor—We thank Heidemann and Clark for their interest in our paper and are pleased to be given an opportunity to reply to their comments. We reject their suggestion that we studied a heterogeneous population. As stated clearly in the text, there was no statistical or clinically relevant difference between the groups we evaluated in terms of age, weight or parity.

As discussed in our manuscript, the incidence of hypotension is influenced by the cut-off level chosen, which is often arbitrary. In the absence of a widely accepted definition for hypotension, our power calculation was based not only the highest incidence reported in previous studies,[1] but also on demonstrating a 30% reduction in the incidence of hypotension, which most practitioners would find clinically relevant. Our study found that phenylephrine 4 mg i.m. and ephedrine 45 mg i.m. reduced the severity of hypotension and the total dose of rescue i.v. ephedrine during anaesthesia for Caesarean section. The distressing side-effects associated with spinal anaesthesia (nausea, vomiting and dizziness) are invariably signs of imminent severe hypotension which may escape detection by non-invasive blood pressure monitoring. However, we did not feel that invasive arterial monitoring, which would have revealed real-time reductions in arterial blood pressure, was justified in this study population. Although we did not record the incidence of these side-effects *per se*, logic suggests that preventing systemic hypotension would also reduce their incidence.

B.T. Ayorinde
D.J Buggy
Leicester, UK

1 Rout CC, Rocke DA, Levin J, Gouws E, Reddy D. A re-evaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anaesthesia for elective Cesarean section. *Anesthesiology* 1993; **79**: 262–9

Epidural catheter associated duritis

Editor—I would like to report an unusual case of severe back pain associated with an indwelling epidural catheter.

A 16-year-old male weighing 59 kg was booked for an elective colectomy for familial polyposis coli. He was previously fit, on no medication, and had normal preoperative investigations. I inserted a 16 gauge epidural catheter at T11/12, leaving 6 cm in the epidural space. A test dose of 3.5 ml of 1% lidocaine with epinephrine 1/200 000 was given without incident. I was later notified that he had received a morning dose of prophylactic low molecular weight heparin 2 h before the epidural insertion despite orders to the contrary.

The anaesthetic consisted of propofol and remifentanil infusions, with a total of 10 ml of 0.5% bupivacaine injected through the epidural catheter. An epidural infusion was commenced intraoperatively using preservative-free ropivacaine (2 mg ml^{-1})-sufentanil (1 μg ml^{-1}) mixture. The intraoperative course was uneventful. On arrival in recovery the patient was pain-free and stable with the epidural infusion running at 8 ml h^{-1}. No epidural boluses were administered during the recovery room stay.

Later that night, the patient experienced an acute onset of severe constant back pain, without any neuropathic features, about 5 cm above the epidural insertion site. No epidural boluses were reported as having been given. Neurological examination revealed no motor or sphincter weakness. Only moderate pain relief was obtained from i.v. ketorolac 30 mg and morphine 30 mg and so, due to persistence of the pain, the catheter was removed 3 h later. The reviewing doctor felt that an urgent MRI scan was unwarranted at that time due to the absence of any neurological signs. The pain continued for the next 72 h, requiring large doses of opioid to achieve satisfactory analgesia, and then gradually subsided. A MRI scan was performed about 20 h after the onset of the pain, and showed a 10 cm region of inflamed dura centred around T9 (Fig. 1). A radiologist was unsure if this was a normal reaction to an epidural catheter or a pathological process causing the pain.

The aetiology of the back pain in this case remains unclear. The possibilities appear to be: pain unrelated to the catheter; an atypical reaction to the catheter or drugs; or an irritant drug having been administered through the epidural catheter. The latter would

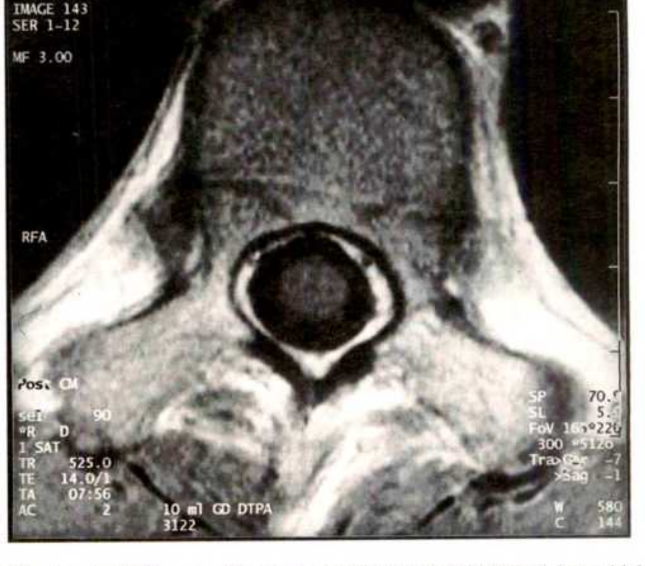

Fig. 1 Axial MRI scan with contrast at T9 showing thickened dura which extended for 10 cm in both directions.

appear to be the most likely explanation due to the initially stable postoperative course, and the acute onset of the pain. However, a recent review article of nine case reports involving incorrect administration of epidural potassium chloride[1] describes predominantly autonomic symptoms with neurological signs without pain. Two case reports published in 1984[2] describe the accidental administration of epidural thiopental; again pain was not a prominent feature of the clinical picture.

While it was pleasing to see the spontaneous resolution of the patient's pain, the lack of a diagnosis remains a concern.

Andrew Imison
Department of Anaesthesia and Pain Medicine
Royal Perth Hospital
Perth
Western Australia

1 Nascimento jr P, Modolo NSP, Meletti JFA, Braz JRC. Sympathetic hyperactivity, respiratory failure, pruritus, and anaesthesia after unintentional epidural injection of potassium chloride: case report. *Reg Anesth Pain Med* 1998; **23**: 219–22
2 Cay DL. Accidental epidural thiopentone. *Anaesth Intensive Care* 1984; **12**: 61–3

Paralysis of the hypoglossal and pharyngeal branches of the vagus nerve after use of a LMA[†] and ETT

Editor—We would like to report a unique case of unilateral paralysis of the hypoglossal and pharyngeal branches of the vagus nerve following use of a laryngeal mask airway (LMA) followed by a tracheal tube (ETT).

A 46-year-old man was admitted for sinus surgery under general anaesthesia. Anaesthetic assessment revealed that he was obese with a body mass index of 33. He had a short neck and a large tongue. Yet there was no significant medical history and he was otherwise fit and healthy.

A technique of total i.v. anaesthesia (TIVA)[1] with propofol, remifentanil and mivacurium was used. A size 4 LMA was inserted with some difficulty due to the anatomical reasons mentioned above. Just enough air was injected into the cuff to secure the airway. Before starting the operation, when the patient's head was lifted for sliding a head ring into position, the LMA was inadvertently displaced. The anaesthetist then inserted an ETT, and TIVA was continued.

The surgery was uneventful, as was the immediate postoperative recovery. About 6 h later, in the ward, the patient complained of impaired tongue movement. He also had difficulty eating and chewing. On examination, the tongue was deviated to the left and was slightly swollen. The soft palate displayed asymmetrical elevation revealing left-sided paresis. The gag reflex was intact, probably because the contralateral efferent nerves were not affected. No other cranial nerves were involved and no other neurological deficiency was found. The only plausible explanation was neuropraxia due to pressure from the LMA. No further investigation was deemed appropriate and the patients was discharged with arrangement for biweekly review.

Lingual nerve injuries[2] and hypoglossal palsies[3] are among the few extremely rare complication reported of using ETT or LMA. In all but one case[4] recovery was complete, corroborating the belief that neuropraxia was the cause of the paralysis. There is no evidence in the literature of the benefits of extensive investigations,[5] and none were carried out in our case. The biweekly reviews in the outpatient clinic postoperatively showed a steady recovery of function over a 6-week period, first of the pharyngeal and then of the hypoglossal branch of the vagus nerve.

Understanding of the course of the hypoglossal nerve and the pharyngeal branch of the vagus nerve may aid us to ascertain the site of the injury and the pathogenesis of the resultant paralysis. The twelfth cranical nerve emerges from the skull through the hypoglossal canal. It then descends between between the internal carotid artery and the internal jugular vein. At the level of the angle of the mandible it becomes superficial and lies just above the greater horn of the hyoid bone.[6] It then crosses the lingual artery running forward over the hyoglossus and passes on to the lateral aspect of the genioglossus, from where it distributes into the substance of the tongue. The inflated cuff of the LMA could lie in close proximity to the base of the tongue and pyriform fossae.[6,7] The pressure in the cuff may increase by 50% during 30 min of anaesthesia with nitrous oxide. The probable site of injury therefore is at the greater horn of the hyoid bone where the inflated cuff of the LMA can compress the nerve against the bone. When using a tracheal tube, pressure from the Mackintosh blade of the laryngoscope at the base of the tongue during intubation might also lead to compression of the hypoglossal nerve between the hypopharynx and the greater horn of the hyoid.[4]

The pharyngeal branch of the vagus arises from the inferior ganglion of the vagus nerve and slopes forward across the internal carotid artery, deep to the external carotid, parallel with and below the glossopharyngeus and joins the pharyngeal plexus on the middle constrictor muscle. In its course, it lies beween the glossopharyngeal nerve above and the hypoglossal nerve below. Normally, it is not proximal enough to the hypoglossal to be at risk. Thus it is postulated that the pharyngeal branch might have run an aberrant course in this patient close to the hypoglossal nerve, resulting in neuropraxia in both nerves. Damage to the pharyngeal branch of the vagus nerve compared to the hypoglossal branch was probably less severe, leading to earlier recovery. As the number of ETTs and LMAs used worldwide is considerable, the complication of such nerve palsies is exceptionally rare.

N. Umapathy
T.G. Eliathamby
M.S. Timms
Blackburn Royal Infirmary
Blackburn
UK

1 Dyer RA, Llewellyn RL, James MF. Total intravenous anaesthesia with propofol and the laryngeal mask for orthopaedic surgery. *Br J Anaesth* 1995; **74**: 123–8
2 Laxton CH, Kipling R. Lingual nerve paralysis following the use of laryngeal mask airway. *Anaesthesia* 1996; **51**: 869–70
3 Reinhold H, Deloof T, Jortay A, Mathieu M, Vandesteene A. The risks of tracheal intubation. *Acta Anesthesiol Belg* 1978; **29**: 69–84
4 Baumgarten V, Jalinski W, Bohm S, Galle E. Hypoglossal nerve palsy following nasal septal surgery. *Der Anesthetist* 1997; **46**: 34–7
5 Sugama S, Matsunga T, Ito F, Eto Y, Maekawa K. Transient unilateral hypoglossal palsy. *Brain Dev* 1992; **14**: 122–3
6 King C, Street MK. Twelfth cranial nerve paralysis following the use of a laryngeal mask airway. *Anaesthesia* 1994; **49**: 786–7
7 Figueredo E, Vivar-Diago M, Munoz-Blanco F. Laryngo-pharyngeal complaints after use of the laryngeal mask airway. *Can J Anaesth* 1999; **46**: 220–5
8 Lee SS, Wang SJ, Fuh JL, Liu HC. Transient unilateral hypoglossal palsy: a case report. *Clin Neurol Neurosurg* 1994; **96**: 148–51

[†] LMA® is the property of Intavant Limited

ProSeal laryngeal mask airway use for prolonged middle ear surgery

Editor—We report the first use of the ProSeal laryngeal mask airway (PLMA†) for ear surgery, and describe the changes in cuff pressure and volume following the use of nitrous oxide anaesthesia in a procedure lasting nearly 5 h.

A 40-year-old male, ASA 1, was scheduled for a mastoid exploration and atticotomy. He gave no history of reflux, weighed 82 kg, was 175 cm in height, and his airway was scored as Mallampatti grade 2. He was unpremedicated and following i.v. induction with fentanyl 100 μg, propofol 200 mg and atracurium 30 mg, bag and mask ventilation was performed with sevoflurane in nitrous oxide/oxygen. A size 4 PLMA was easily inserted at the first attempt using the recommended technique[1] by a consultant with extensive experience of the flexible laryngeal mask airway (FLMA). The cuff was inflated to a pressure of 60 cm H_2O[1] with a cuff inflator/pressure gauge (Portex, Juningen, Germany) corresponding to 32 ml of air. Oropharyngeal leak pressure[2] was 33 cm H_2O in the neutral, left and right head positions. Endoscopic views down the laryngeal tube were grade 4 (only vocal cords seen)[3 4] in all three head positions.

Volume-controlled intermittent positive pressure ventilation (IPPV) was instituted through a circle system (Ohmeda 7900, Oatex Ohmeda, Madison, WI, USA) with tidal volumes of 530–600 ml, an I:E ratio of 1:2 and a rate of 12 min^{-1}; peak airway pressures were 14–17 cm H_2O throughout. To facilitate facial nerve monitoring no further muscle relaxants were given. Gas mixtures were: $F_{I_{O_2}}$0.35–0.4, ET sevoflurane 2.1–3.4%, E'_{CO_2} 5.1–6.1 kPa and fresh gas flow between 500–800 ml min^{-1}. Systolic blood pressure was kept between 80–90 mm Hg with a pulse of 50–60 beats min^{-1}, using a total of labetalol 20 mg. Oxygen saturations were 97–99% throughout, 15° head-up was used and 2000 ml of crystalloid were given. Diclofenac 75 mg i.v., morphine 5 mg i.v., dexamethasone 8 mg and ondansetron 4 mg were also administered.

Surgery lasted 4 h 40 min and operating conditions were described as very good. At the end of the procedure an examination of the other ear was performed, and an extensive bandage was wrapped around the head requiring considerable head movement. Prior to discontinuation of anaesthesia, the cuff pressure was measured as 110 cm H_2O with a cuff volume of 38 ml. Fibrescopic views were identical to those at the start of anaesthesia and a 14 G gastric tube was easily passed down the oesophageal vent, draining 6 ml of clear fluid and no air. Anaesthesia was discontinued and, once spontaneous respiration had resumed, the patient was transferred to recovery with the PLMA *in situ*. Fifteen min later, the patient was awake and the PLMA was rejected quietly and smoothly, with no coughing or gagging. On review the next morning, the patient volunteered how well he felt and reported no sickness or sore throat; subjectively his voice was of normal character. He was discharged an hour later, 15 h after surgery.

The use of the FLMA for ENT procedures is well established,[5] and its advantages over the tracheal tube include: avoidance of laryngoscopy, less invasion of the respiratory tract, avoidance of the risks of endobronchial or oesophageal intubation, less trauma to local tissues, and a lower incidence of coughing, straining and breath-holding during emergence.[6–8]

The PLMA is a new laryngeal mask device with a larger cuff and an oesophageal drainage tube. The intention is to ensure correct placement and facilitate safe IPPV.[1] Brimacombe and Keller have shown that directly measured mucosal pressures are similar between the LMA† and PLMA for a given cuff volume. However, the directly measured mucosal pressure is lower with the PLMA for a given oropharyngeal leak pressure.[9]

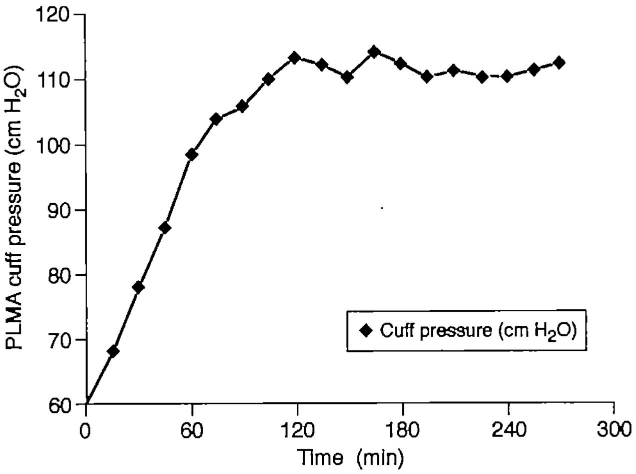

Fig. 1 Change in PLMA cuff pressure over time.

In this case the PLMA intracuff pressure was noted at 15 min intervals (Fig. 1). The intracuff pressure rose rapidly from 60 cm H_2O at the start to 98 cm H_2O after 1 h, peaking by 2 h at nearly double the starting pressure, presumably from nitrous oxide diffusion. Brimacombe and Keller[9] found that cuff volume, *in vivo* intracuff pressures, and calculated mucosal pressures were an imprecise predictor of directly-measured mucosal pressure. We introduced 32 ml of air at insertion corresponding to 60 cm H_2O intracuff pressure and found that the oropharyngeal leak pressure (OLP) was 33 cm H_2O. More recent work suggests that the OLP increases most markedly from 0 to 10 ml cuff volume.[9] Further volumes added little extra benefit.

M. Nicholls
A. Patel
London

1 Brain AIJ, Verghese C, Strube PJ. THe LMA 'ProSeal'—a laryngeal mask with an oesophageal vent. *Br J Anaesth* 2000; **84**: 650–4
2 Keller C, Brimacombe J, Keller K, Morris R. A comparison of four methods for assessing airway sealing pressure with the laryngeal mask airway in adult patients. *Br J Anaesth* 1999; **82**: 286–7
3 Brimacombe J, Berry A. A proposed fibre-optic scoring system to standardize the assessment of LMA position. *Anaesth Analg* 1993; **76**: 457
4 Joshi S, Sciaca RR, Solanki DR, Young WL, Mathru MM. A prospective evaluation of clinical tests for placement of laryngeal mask airways. *Anaesthesiology* 1998; **89**: 1141–6
5 Nair I, Bailey PM. Review of uses of the laryngeal mask airway in ENT anaesthesia. *Anaesthesia* 1995; **50**: 898–900
6 Brimacombe J, Brain A. Advantages and disadvantages. In : Brimacombe J, Brain A, eds. *The laryngeal mask airway, a review and practical guide.* London: Saunders, 1997; 107
7 Holden R, Morsman CD, Butler J, Clark GS, Hughes DS, Bacon PJ. Intraocular pressure changes using the laryngeal mask airway and tracheal tube. *Anaesthesia* 1991; **46**: 922–4
8 Akhtar TM, McMurray P, Kerr WJ, Kenny GNC. A comparison of laryngeal mask airway with tracheal tube for intra-ocular opthalmic surgery. *Anaesthesia* 1992; **47**: 668–71

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9 Keller C, Brimacombe J. Mucosal pressure and oropharyngeal leak pressure with the ProSeal versus laryngeal mask airway in anaesthetized, paralysed patients. *Br J Anaesth* 2000; **85**: 262–6

Protecting anaesthetic tubing from occlusion

Editor—I was interested to read the letter from Drs Dell and Cochrane[1] published recently in the *British Journal of Anaesthesia*, on the use of pipe sections around the wheels of anaesthetic machines to prevent pipelines, electric cables and scavenging tubing being run over and interfering with the movement of anaesthetic machines.

Your readers may be interested to hear that this technique has been used in our department in Japan for more than one decade and was published in 1994.[2]

T. Sakai
Department of Anaesthesia,
University of Hirosaki,
School of Medicine, Hirosaki,
Japan

1 Dell R, Cochrane D. Protecting anaesthetic tubing from occlusion. *Br J Anaesth* 2000; **84**: 698
2 Sakai T, McIntyre JWR, Baba S, Matsuki A. Push and pull: Move your anaesthesia machine more easily. *Anesth Analg* 1994; **79**: 196–7

British Journal of Anaesthesia 87 (2): 325–8 (2001)

Book Reviews

Awareness During Anesthesia. M.M. Ghoneim (editor). Published by Butterworth Heinemann, Oxford. Price £40. ISBN 0750672013.

It is unusual when the preface to a textbook makes interesting reading. The preface to *Awareness During Anesthesia* is not only interesting but is also so extensive and informative as to be almost a chapter in itself. This promising start sets the tone for the rest of the book where acknowledged experts in anaesthesia and psychology provide an excellent account of the current state of the art in this difficult area of research.

Four chapters address the monitoring of anaesthesia, the detection of awareness and its relationship to post-anaesthetic memory, whilst a further four describe learning and memory during anaesthesia and the psychological consequences. A final chapter reviews the medico-legal consequences of awareness. All chapters are well written and while some detail of memory test procedures is repeated as the different authors describe various empirical studies, it has the virtue of allowing chapters to stand alone and be understood by the browsing reader.

The opening chapters by Ghoneim provide a comprehensive historical perspective and an indepth description of the phenomenon of awareness and the occurrence of implicit and explicit memories for events during anaesthesia. The approach is constructively critical of past research where, as the editor notes, quite contradictory results are found across studies. These chapters provide an excellent grounding for readers who may be unfamiliar with the field of research.

Whilst all the authors agree that the investigation of memory during anaesthesia depends upon reliable control of the depth of anaesthesia, perhaps predictably they differ in their conclusions as to the optimal measures. Jones and Aggarwal provide an expert review of EEG methods of monitoring awareness and observe the potential promise of the bispectral analysis (BIS), the auditory evoked response (AER), and the coherent frequency of the AER. They note that standard comparisons are required between the methods, and the cognitive outcomes. They also conclude that the routine use of monitoring devices may be difficult to justify in view of the apparent rarity of awareness and the cost of such disposable items as electrodes. The relationships of BIS to memory during anaesthesia is considered in detail by Kerssens and Sebel whose careful review concludes with the important observation that, as anaesthesia is deepened, sub-cortical learning and memory may occur which would not be effectively detected by BIS (and also becomes a challenge for detection by psychological tests).

Thornton reviews studies of the AER to conclude that memory formation does not occur in anaesthetized (unconscious) patients, and hence that the recall of intraoperative events would be unlikely. She also concludes that whilst a correlation between the AER and memory is elusive, the AER may still serve the function of preventing explicit memories because it distinguishes between conscious and unconscious states. Readers of an over-sensitive disposition might be distressed by Dr. Thornton's inclusion of the 'Rottweiler-social-worker' joke (it is relevant in the context of her research: read the book and find out) but, for the record, it amused your insensitive reviewer.

The isolated-forearm technique is well reviewed by Russell who provides strong argument and evidence to overcome misconceptions about its use. Russell also makes a telling observation about the neglect of individual variation in some monitoring. He cites the BIS where group-average values correlate well with group-average consciousness levels, but observes that individual variation is such that individuals may recover consciousness across a BIS range of 60–90 (Jones and Aggarwal, and Kerssens and Sebel, make related observations). Clearly, such variation makes it difficult to establish a convincing absolute value as a cut-off between consciousness and unconsciousness.

Andrade provides a thoughtful account of learning during sedation and anaesthesia from the standpoint of a cognitive psychologist. She reviews her experimental work to conclude that the evidence for learning during anaesthesia is equivocal. She suggests, however, that the release of catecholamines in response to stress and surgery may facilitate memory, hence explaining the tendency for negative results to be found in studies using non-surgical volunteers. Wang, a clinical psychologist, extends investigation to the emotional consequences of awareness and memory for anaesthesia. Whilst there is evidence for post-traumatic stress disorder consequent on frank memories of intraoperative events, Wang also demonstrates psychopathology in patients whose anaesthesia was 'light' (but with no conscious recall or complaint of awareness) when compared to those with deeper anaesthesia. If these intriguing results can be replicated, they raise the possibility of implicit emotional learning in the absence of apparent awareness that may have implications for postoperative mental health.

Wang's results may be relevant to discussion by Domino and Aitkenhead in their incisive and far-ranging coverage of the medico-legal consequences of awareness which encompasses the UK, Europe and the USA. As the editor points out in his preface, their chapter describes a 'compendium of aetiologies' which provides the means to predict and avoid events that might otherwise lead to catastrophe and litigation.

In summary, *Awareness During Anesthesia* provides a thoroughly comprehensive, up-to-date and expert analysis of the topic of awareness and memory for events occurring during anaesthesia. It deserves a wide readership across the many specialities encompassed within anaesthesia and psychology. It not only informs clinical practice but also demonstrates effective research collaboration between the two very different disciplines of anaesthesia and psychology. It will undoubtedly stimulate more research by practitioners in both disciplines.

Keith Millar
Department of Psychological Medicine
University of Glasgow Faculty of Medicine
Glasgow, UK

Pain Imaging. K.L. Casey and C. Bushnell (editors). Published by IASP Press, Seattle. Pp. 248; indexed; illustrated. Price $89. ISBN 0-931092-34-5.

The concept of this book cannot be welcomed too vigorously. The book relates and demonstrates the coalescence of anatomy, physiology and the psychology of pain. The figures and plates show the sites and relative intensity of activity of the spinal cord and brain during periods of nociceptive stimuli or during the perception of pain or both. It shows how the activity of these parts of the brain can be inhibited by distraction, hypnosis, relaxation and analgesics and shows the interrelation of the activity of different parts of the brain. It also describes how the activity of the nervous system can be imaged and why this is possible. All this it achieves in less than 250 pages.

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Since there have been great advances in optical imaging, positronic emission tomography, and functional magnetic resonance imaging, as well as in animal autoradiography in the last two decades, there are two inferences: that it is unlikely that there will ever again be a book as compact and as comprehensive as this, and that this is, at least in parts, concentrated reading. Indeed the book is in two kinds of parts: there are parts which are concentrated but a fascinating exposition of how the pain-related nervous system works and how it can be seen to function; and there are parts which are of unfamiliar concepts in unfamiliar language. The size and position of this second kind will vary depending on the background knowledge of the reader and may be non-existent for the experimental neuroscientist.

The book starts with a clear, concise and comprehensive overview by Ken Casey of pain mechanisms, pathways and problems, and of the contribution of the various forms of imaging. This alone is worth the price of the book. There follows the rationale for the association of the imaging techniques and the function of the neurones and their synapses—the association between activity and blood flow, glucose uptake, alteration of haemoglobin and changes within the cellular microenvironment. The chapter on optical imaging of near infra-red absorption is concerned mostly with a non-traditional concept of the activity and interactions of different parts of the primary somatosensory cortex, but it left me wondering how sensitive, localized or robust this method is. There follow technical chapters of single photon emission computed tomography (SPECT), and positronic emission tomography (PET), and of functional MRI, each followed by chapters describing studies of pain using these imaging techniques. Finally, there is one of functional imaging of animal preparations using either these techniques or autoradiography.

For me, as a generalist pain clinican, the technical aspects of PET, SPECT and MRI were difficult to understand but the pain studies were interesting and revealing, fitting together pieces of the jigsaw of experimental findings and clinical observations of pain perception. The technical chapters assumed a use of language which would not be familiar to most clinicians or to many radiologists. A top-grade medical physicist will be able to provide clear explanations of many of the terms and concepts that were not explained in the text. I was grateful for the summary at the end of each chapter. The broad concepts are more easily understandable and the detail is not essential to the understanding of the studies of imaging. Karen Davis, for example, gives a three-page summary of how functional MRI works at the beginning of her chapter on the studies of pain. As a poor student of neuroanatomy, I would have appreciated anatomical drawing annotated with the acronyms used throughout the text. Since acroynms may have more than one meaning, especially in other disciplines, a glossary at the the beginning of the book would have been useful, especially for those wishing to use this as a reference book. Although the book is rich in diagrams, even more are required for generally unfamiliar ideas, processes and anatomy.

I have two complaints with the publishers. The house style of referencing to include the first author's name and date in the text may be useful to lend immediate authority to the statements, but the use of two or three lines of references within the sentence can lose the flow of prose, and to have two such sets of references within the sentence can cause the reader to search for the meaning of the sentence. The second complaint is of the index which is less than inclusive.

I found this a fascinating book, difficult to follow in parts and requiring re-reading in sections sometimes because the words are unfamiliar but also because the implications in other contexts are exciting and the mind tends to wander from the text. This is a glimpse of the future, of a way by which therapies will be introduced and assessed, of a greater understanding of pain and of the inter-relationships of the various disciplines of pain therapy. I was surprised how much the message of this book influenced my way of thinking about pain problems in clinical practice and my confidence in explaining the problems of diagnosis and treatment to my patients. This is not just for academic physiologists and neuroscientists, this is for everyone, pain clinicians, rheumatologists, gastroenterologists and others, who wish to see and comprehend their subject. Even if the knowledge is not easily assimilated, it will be greatly valued.

John Alexander
Bristol, UK

Notes in Neuroanaesthesia and Critical care. (1st edn). A.K. Gupta and A. Summors. Published by Greenwich Medical Media Ltd, London. Pp 302; indexed; illustrated. Price £24.50. ISBN 1841100358.

The authors state that this book is intended to provide essential information and key references to help trainees obtain the necessary knowledge for their FRCA examination. It is also suggested that it will be useful for revision for practising anaesthetists and for medical and nursing staff in intensive care units, junior doctors in neurology and neurosurgery, medical students, and staff in non-neurosurgical centres who manage neurologically injured patients and need to transfer patients to neurosurgical units. In attempting to appeal to this very wide range of readers, the authors have produced a book which is not ideally suited to any.

The first thing that strikes the reader is the layout which is very wasteful of paper. There is a title page for each chapter in the seven sections of the book, often with a blank page preceding the title page. Thus, two pages are wasted each time title pages are provided. This is superfluous because there is a comprehensive list of contents at the beginning of the book. Despite these criticisms, the breaking up of topics into short chapters of up to four pages in length is a good idea because the largely very comprehensive information is delivered very concisely. This is enhanced by the provision of a list of key points at the end of every chapter and suggested further reading.

There is a degree of repetition of information because of this format. Linking shunts to paediatric anaesthesia and combining all the chapters on head injury would help. alternatively, more cross-referencing could be used. In the interests of brevity the chapters are didactic and not everyone will agree with some of the statements made. For example, the interpretation of the literature regarding the effects of various anaesthetic agents on the production of CSF differs from my own and there is no mention of the effect on ICP of involuntary muscle activity with etomidate. The use of paracetamol as a co-analgesic is not mentioned in chapter 12. No reasons are given in chapter 16 for preferring TIVA to volatile agents in patients with large acoustic neuromas and I would question the wisdom of using nitrous oxide during carotid endarterectomy because of its effect on cerebral metabolic rate. Also, I do not understand why rapid awakening after neurosurgery in pregnancy should carry a risk of aspiration unless there is bulbar palsy; surely rapid awakening reduces the risk of aspiration.

I particularly enjoyed reading the chapters on: nursing issues, which will help trainees to see the nurses point of view; the EEG, which gives the most succinct and informative explanation of the EEG that I have seen to date; and neuroimaging. The latter chapter could usefully be expanded to explain MRI. However, I would question the value of the very brief chapter on nerves, anatomy and function, and those on muscular dystrophies, myasthenia and stroke. These topics are dealt with very well in standard textbooks and seem out of place in this book.

There are some spelling mistakes and, in chapter 53, there seems to be a section missing after hypocapnia because the paragraph following this heading does not relate to this subject. In addition, there is an error in the equations on page 227 and an increase, not decrease, in PaO_2 is required to increase oxygen delivery (Fig. 53.2).

There is a wealth of useful information in this book but, in my opinion, it does not achieve its stated objectives. It is not significantly shorter than some other, more detailed textbooks on neuroanaesthesia and neurointensive care which candidates preparing for the FRCA would find more useful. If some of the chapters were combined, and the book shortened significantly, it would be appropriate for preparation for the FRCA and for medical and nursing staff in intensive care units. Individual chapters would form a useful basis for in-theatre teaching but most neuroanaesthetists have similar notes on which they base their teaching. The book is too elementary and didactic for neuroanaesthetists and neurointensivists wanting to update their knowledge. I would recommend one of several larger textbooks on neuroanaesthesia and neurointensive care for this purpose.

E.Moss
Leeds

International Anesthesiology Clinics. W.E. Hurford (editor-in-chief). Vol. 39; 2001: *Current Issues in Anesthesiology 2.* W.E. Hurford and L.I. Gilbertson (editors). Published by Lippincott, Williams and Wilkins Philadelphia. Pp. 146; indexed; illustrated. Price $74($228 annual subscription) ISSN 0020-5907.

The Clinics were started in Boston, USA in August 1962 and were to provide clinically relevant material in a direct, easy to comprehend manner and to provide the commission with authoritative advice (while it is still fresh) that can be put to use in their clinical practice. Indeed, the original editors suggested that the Clinic should provide enjoyable and relaxing reading as well as practical information. To achieve this aim the format was planned with easily read, large type and ample illustration.

The current editorial team are also based in Boston. This volume is the second on the topic of 'Current Issues in Anesthesiology'. The first was published in the latter part of 2000. The wide variability in topics discussed in the first issue has been continued into the current volume. The nine chapters present can be divided into those related to coagulation or renal-splanchic problems, with a single chapter related to the ventilatory management of patients with severe asthma. The latter is probably one of the weaker chapters in the collection. The author failed to discuss any of the currently available techniques for controlled ventilation but mainly offers the advice that you get fewer problems it you give the patient time to breath out! The author also suggests that the ventilator gas can be changed to a mixture of 60% helium and 40% oxygen. This reviewer is unaware of any of the currently available modern ventilators used in intensive care that will provide this facility.

The remaining sections of this journal do, however, make up for this weak section. In particular the chapters on thrombelastography (the correct spelling as opposed to the instance among Americans of adding an O after the B), and continuous renal replacement therapies are excellent example of authoritative adive in a relaxed reading style. Both articles discuss relatively uncommon areas which affect the anaesthetist, and provide excellent examples of how to provide an overview of a complex subject in a concise form. This is also true for the chapter about abdominal compartment syndrome, which appears to be a new way of looking at an old problem. Four of the remaining chapters discuss and review a number of older topics. Nonetheless, I think that they form the basis for excellent teaching material and journal club type reviews by junior staff. These chapters are on a number of diverse topics including low platelet count, the use of neuroaxial blockade in the patient receiving anticoagulation, perioperative renal replacement therapy, and the renal dopamine controversy.

Overall, I think that this issue of the Clinic fulfils the ambition of the editor very well. This reviewer spent about four hours in total reading the whole book and noted about eight articles and references to follow up as continued reading. The Clinics are very easy to read and can be picked up and read as a 'coffee table' booklet. The major concern is that the series are only available as a subscription. The current editors have not continued with the tradition of highlighting future topics. The reader, or their library, could therefore end up subscribing to a journal which has a reduced relevance due to either the choice of topic or the author. Overall I would think that most practitioners would consider that this is a journal for the library. I would certainly go along with that point of view.

D. Royston
Middlesex

Advanced Paediatric Life Support: The Practical Approach. (3rd edn). K. Mackway Jones, E. Molyneux, B. Phillips, S. Wieteska (editors). Published by BMJ Books, London. Pp. 336; indexed; illustrated. Price £25. ISBN 0727915541.

When reviewing this book it is difficult to separate it in one's mind from the excellent 3-day APLS Course for which it is written as the course reference text and syllabus. The book now appears in its third edition, being first published in 1993, and its publication coincides with changes in the course. The format of the book closely follows the content of the course having sections on life support techniques, the seriously ill and seriously injured child, and a section describing life-saving practical procedures necessary to treat sick children. This book is also used on the shorter 1-day PLS Course and the authors have cleverly indicated which chapters should be studied by these candidates by putting a grey flash on the leading edge of relevant chapters.

This new edition has been written to incorporate new evidence-bases, international guidelines drafted by ILCOR (International Liaison Committee on Resuscitation). These particularly affect the chapters dealing with life support and arrhythmia management, which contain clear ECG traces of each arrhythmia followed by a flow diagram of the appropriate protocol to manage it. Each arryhthmia also has commentary text describing the protocol and in most cases the rationale behind each treatment step. There is discussion on areas of current debate, for instance the use of Automated External Defibrillators (AED) and biphasic waveforms in childhood VF/pulseless VT. In this edition, the authors have again decided not to include references at the end of each chapter and although this is contrary to most medical texts it can be justified by the claim to be a functional text, written to appeal not only to medically trained staff but to other paramedical staff for whom such information may not necessarily be of use. However, for those interested, the authors have set up a web site: *www.bestbet.org* on which they claim will be up-to-date references and other consensus evidence for particular treatment regimens and protocols.

The chapters dealing with the seriously ill child have been completely revised for this edition with each chapter emphasizing the presenting complaint of the child and its treatment; for example, 'The child with breathing difficulties' or 'The child in shock'. This is an improvement on the previous editions that had the traditional approach of dealing with conditions by physiological systems. This new 'presenting complaint based' approach means that the information is more readily available as a reference for staff dealing with unfamiliar situations in children. Indeed this reflects the way that any clinician, however experienced, deals with a given clinical situation. The chapters dealing with the seriously injured child and practical procedures are little changed from previous editions with the exception of 'Interpreting trauma x-rays', which now includes several well-drawn and useful illustrations as well as concise text.

The final section of the book contains appendices on a wide range of subjects from interpretation of acid-base to triage and even management of envenomation. The latter appendix has been added to reflect the worldwide spread of the APLS Course; many European Countries as well as Australia and recently South Africa have embraced it. Of interest to the anaesthetist are the appendices on 'Child abuse' and 'Dealing with death.' These are both areas of medicine not previously given high enough priority but with which anaesthetists can be involved. The child abuse section gives the reader a brief overview of the classification of child abuse, the management strategies, and the medicolegal aspects of the various court orders available to protect vulnerable children. Although this chapter is no substitute for knowing local procedures at one's own institution it gives the reader food for thought. Dealing with death is always difficult but never more so than when children are involved. This appendix, although brief, provides practical advice on breaking bad news to parents as well as a useful checklist of what needs to be done after such an event.

In conclusion, this text is intelligently written and contains many new and some improved illustrations. The new format for the chapters on critical illness make this text essential to any anaesthetic departmental library and it should be available to staff 24 h a day. This is especially so for departments dealing with children on a less frequent basis. I would highly recommend this book to all anaesthetisits who have any responsibility for looking after children. However, instead of buying a copy, I urge all readers to go the 3-day APLS course where the book will be given to you free of charge with the pre-course information pack!

R. Perkins
Manchester

Problems in Anesthesia Series. L.A. Fleisher and D.S. Prough (editors-in-chief). *Airway Management.* A. Ovassapian and D.W. Coalson (guest editors). Published by Lippincott, Williams and Wilkins, London. Pp. 108; illustrated. ISSN 0889-4698.

This is a short (108 page) American textbook covering the important aspects of airway management. Management of the difficult airway continues to be a challenge to all anaesthetists and this review is a helpful addition to existing knowledge.

The initial chapter provides a review of respiratory physiology and the basics of oxygen and carbon dioxide transport. The next few chapters are devoted to airway management with and without a tracheal tube. The laryngeal mask airway (LMA[†]) has a chapter devoted to its impact on airway management, and the different types of LMA are clearly described. The specialized uses for the LMA are detailed, especially its important role in the management of the difficult airway. Its use in specialized situations, including neurosurgical anaesthesia, is described; however, this is not an area where it has widespread use certainly in my institution. The recently introduced ProSeal LMA is discussed, as are its advantages for positive pressure ventilation.

Other well-known methods of airway ventilation without the use of an tracheal tube are detailed including the cuffed oropharyngeal airway, the oesophageal obturator airway, and the oesophageal Combitube.

The text then considers artificial ventilation using a tracheal tube and first deals comprehensively with the prediction of difficult intubation. This chapter usefully describes the physical signs known to be associated with difficult intubation. The scoring systems to evaluate the airway and predict difficulty associated with tracheal intubation are well described. The variety of methods that can be used as adjuncts in a patient with a difficult airway, including use of the gum elastic bougie, are given. (The intubating LMA is described in earlier chapters).

As you might expect with such expert authors, the techniques of fibreoptic intubation have a comprehensive and authoritative description. There is a useful chapter outlining techniques and drugs used for sedation during awake fibreoptic intubation. However, target-controlled propofol is not mentioned and there is only limited discussion on the role or remifentanil, a drug which is gaining popularity in the UK to facilitate awake fibreoptic intubation.

Further chapters discuss other important areas including the problems associated with airway management outside the operating room, and some of the practical airway management problems that may arise in areas such as the intensive care unit. One-lung ventilation and the difficult airway is described, as well as management of the difficult airway in the pregnant patient.

This is a useful and comprehensive book that will have something of interest for all anaesthetists.

J.A. Langton
Devon
UK

[†] LMA® is the property of Intavant Limited

British Journal of Anaesthesia **87** (2): 329 (2001)

Erratum

Effects of haemoglobin-based oxygen carrier Hemoglobin glutamer-200 (bovine) on intestinal perfusion and oxygenation in a canine hypovolaemia model (BJA 2001; 86: 683–92)

Systemic haemodynamic data (page 686, Results, Table 2), CaO_2 (ml dl^{-1}), SaO_2 (%) and sVO_2 (ml min^{-1}) data (page 687, Table 3), and systemic O_2 delivery data (page 687, Figure 2) were originally published by the authors in a recent study analysing systemic effects of Hemoglobin glutamer-200 (bovine) in the **same group** of animals (Driessen B, Jahr JS, Lurie F, Gunther RA. Inadequacy of low-volume resuscitation with hemoglobin-based oxygen carrier hemoglobin glutamer-200 (bovine) in canine hypovolemia. *Journal of Veterinary Pharmacology & Therapeutics* 2001; **24**: 61–71). These data were included to facilitate a comparison of the core data of the present investigation, i.e. data on intestinal perfusion and oxygenation, with those recorded in the systemic circulation.

The authors apologize for having omitted the above-mentioned reference in their *BJA* article and for the confusion that the duplication of data might have caused among readers.

B. Driessen
Kennett Square, PA
J. S. Jahr
F. Lurie
Sacramento, CA
S. M. Griffey
Davis, CA
R. A. Gunther
Sacramento, CA
USA

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BJA

ABSTRACTS

Proceedings of the Intensive Care Society and Riverside Group 'State of the Art' Meeting

South Bank Centre, London

December 7–8, 2000

(The name of the presenting author is shown in bold type.)

FREE PAPER PRESENTATIONS

Rehabilitation after critical illness: a randomized, controlled trial

C. Jones[1], P. Skirrow[1], R. D. Griffiths[1], G. Humphris[2], S. Dawson[3], P. White[3], J. Eddleston[3], C. Waldmann[4], M. Gager[4], H. Hutchinson[4] and A. Lloyd[4]

[1]Intensive Care Unit, Whiston Hospital, Prescot L35 5DR, UK and Department of Medicine, University of Liverpool, Liverpool L69 3GA, UK. [2]Department of Clinical Psychology, University of Liverpool, Liverpool L69 3BX, UK. [3]Intensive Care Unit, Manchester Royal Infirmary, Manchester M13 9WL. [4]ICU, Royal Berkshire Hospital, Reading, UK

Patients recovering from critical illness frequently display high levels of anxiety, depression and symptoms of post-traumatic stress disorder (PTSD).[1] In addition, they display profound muscle weakness, which affects many day-to-day activities.[2] Research into rehabilitation after critical illness is limited, despite the benefits shown of rehabilitation programmes in other patient groups, such as chronic obstructive pulmonary disease and myocardial infarction. The aim of the study was to assess the impact of a self-help rehabilitation package on physical and psychological recovery by 6 months post-ICU.

The study was a block randomized, controlled trial, blind at follow-up. Three intensive care units (ICU) took part. Patients recovering from critical illness were recruited 1–2 weeks post-ICU discharge and allocated to control or intervention group using a sealed envelope technique. All three ICUs taking part run ward and clinic follow-up, so the 6-week rehabilitation programme was tested against the routine follow-up of patients. A separate researcher at each site, who was blind to the patients' study group, completed follow-up questionnaires with the patients at 8 weeks and 6 months post-ICU discharge. The Short Form 36 (SF-36) Health survey, Hospital Anxiety and Depression Scale (HAD), Impact of Events Scale and Fear Index were used to assess physical and psychological recovery. At one study site (Whiston), patients also completed an ICU Memory tool at 2, 8, and 24 weeks.

Of the 126 patients recruited to the study, 69 were intervention and 57 were controls. Ten patients died before the 6-month follow-up, five intervention and five controls. Fifty-eight to sixty-nine (84% intervention and 44/57 (77%)) completed the 6-month follow-up. The clinical characteristics of the patients in the two study groups were well matched.

The intervention group had significantly better SF-36 physical function scores at 8 weeks and 6 months (repeated measures ANOVA, controlled for length of ICU stay, P=0.006). Twelve per cent of intervention patients were shown to be suffering from depression at 8 weeks post-ICU (HAD $\geq$11) *vs* 25% of controls (Fisher's Exact Test, P=0.066). However, other indicators of psychological distress were not significantly different between the study groups. When the cohort of patients with data on memories of ICU were analysed, those patients recalling delusional memories, such as hallucinations, regardless of study group showed the highest levels anxiety and PTSD-related symptoms at 6 months.

A rehabilitation programme in the first few weeks of recovery has significant impact on physical recovery and depression levels. However, the presence of delusional memories confounds any effect of other indicators of psychological distress. Further work is needed to investigate the best way to help patients to cope with memories of delusions.

Keyword: recovery

References

1 Jones C, Humphris GM, Griffiths RD. *Clin Intensive Care* 1998; **9**: 199–205

2 Jones C, Griffiths RD. *Clin Intensive Care* 2000; **11**: 35–8

Measurement of trans-diaphragmatic pressure in ventilated critically ill patients with multi-organ failure by phrenic nerve stimulation and balloon manometry, and its relationship to ventilator independence

M. Longshaw and N. Harper

Critical Care Unit, Manchester Royal Infirmary, Manchester M13 9WL, UK

Measurement of trans-diaphragmatic pressure (Pdi) is an established tool for measuring diaphragmatic strength. Transcutaneous phrenic nerve stimulation has been shown to be a reproducible method for inducing diaphragmatic contraction.[1] Together the techniques can be used to assess diaphragmatic strength in the anaesthetized patient. We investigated whether there was a relationship between induced twitch Pdi and the time taken until ventilator independence in a group of patients with multi-organ failure (MOF).

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We investigated 10 consecutive patients admitted to our critical care unit with MOF. We excluded patients with severe gastric and oesophageal disease, and peripheral nerve stimulation was performed to ensure there were no late effects from the previous use of neuromuscular blocking agents.

Patients were entered into our study at the point where their oxygen requirements, ventilator settings, and metabolic status suggested that they could begin the process of weaning from ventilation. These criteria were: $F\mathrm{I}_{\mathrm{O}_2}<0.6$, inspiratory pressure on pressure controlled ventilation <16 cm water, PEEP <6 cm water, conventional ratio ventilation, absence of metabolic acidosis and mean arterial pressure >70 mm Hg without inotropic support.

We passed balloon-tipped oesophageal and gastric manometry catheters and checked their position by the typical waveforms during respiration. We stimulated the left phrenic nerve in the neck with a Disa Neuromatic neuromyograph in ENS mode at low frequency (<0.5 Hz). The stimulus intensity was increased to a maximum of 100 mA until supramaximal stimulation was achieved, as demonstrated by Pdi max.

We found a strong inverse relationship between induced Pdi and days taken to ventilator independence (r=−0.67). This relationship was independent of skin impedence.

Patients with MOF often have an unpredictable response to weaning, and we propose that this relatively simple technique can be used to identify those patients with impaired diaphragmatic function who go on to have a prolonged period of ventilator dependence.

Keywords: ventilation, mechanical; complications, multi-organ failure

Reference

1 Hamnegard CH, Wragg SD, Mills GH, *et al. Thorax* 1996; **51**: 1239–42

Excessive noise pollution in the Paediatric Intensive Care Unit

R. H. AL-Samsam and P. Cullen

Paediatric Intensive Care Unit, Royal Hospital for Sick Children, Dalnair Street, Glasgow G3 8SJ, UK

The issue of hospital noise pollution has received growing attention in the medical literature because of the increased evidence of its significant health effects. Noise induces many physiological and psychological side effects, such as hearing impairment, interference with speech communication, disturbance of sleep, and elevated diastolic arterial pressure. Although the International Health Council has recommended that noise levels in hospital acute care areas should not exceed 45 dB(A) in the daytime and 20 dB(A) at night, several studies have shown the violation of these levels in various intensive care areas.

The aim of this study was to investigate the noise levels in a tertiary care Paediatric Intensive Care Unit (PICU). The PICU is an open plan unit with seven beds plus three cubicles and a 4-bed bay. The environmental noise was continuously recorded for 48-h using a noise dosimeter (model Q-300, Quest technology). The A-weighted decibel scale dB(A) was used. The microphone was placed near the head of patients in various clinical settings within different locations: A, ECMO; B, haemofiltration; C, mechanical ventilation; D, oscillation; E, humidified oxygen by face mask; and at F, nursing station. A, B, C and F were in the open plan unit while D and E were in a cubicle.

The Q-300 measured the highest sound pressure level (MAX) that occurs during each minute over the 48-h period. MAX values occurring in the same time point of each 24-h were averaged for each location and separated into day (06:00 – 12 mn) and night (12 mn – 06:00) as shown in the Figure 1.

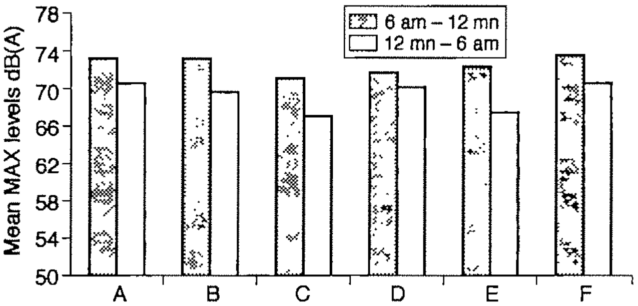

Fig 1 Mean maximum sound levels at different sites within PICU. A = ECMO; B = haemofiltration; C = mechanical ventilation; D = oscillation; E = humidified oxygen by mask; F = nurses station.

Mean levels were significantly lower (P<0.05) at night in all settings. MAX sound pressure levels remained above 59 dB(A) at any given time in all locations.

Noise pollution during the 24-h period was dramatically higher than is recommended for the well being of both patients and staff. The clinical scenario (A/C) had more impact on noise than the physical location (C/D).

Keywords: intensive care, paediatric; complications, noise

A prospective, observational study of ARDS in a cohort of patients in Scottish Intensive Care Units

M. Hughes[1], F. N. MacKirdy[1 2], J. Ross[1], J. Norrie[3] and I. S. Grant[1]

[1]Scottish Intensive Care Society Audit Group (SICSAG), Anaesthetic Department, Victoria Infirmary, Glasgow G42 9TY, UK. [2]Departments of Public Health and Midwifery Studies, University of Glasgow, Glasgow, UK. [3]Robertson Centre For Biostatistics, University of Glasgow, Glasgow, UK

Acute Respiratory Distress Syndrome (ARDS) has been recognized for over 30 yr, yet epidemiological data are still relatively sparse, and published mortality figures vary widely.[1 2] The Scottish Intensive Care Society is currently assessing the incidence of ARDS in its adult Intensive Care Unit (ICU) population, the underlying condition, treatment regimens, mortality and outcome in terms of pulmonary function and quality of life post-discharge.

Twenty-three adult general ICUs participated. Ward Watcher software (Critical Care Audit Ltd) identified all patients with ARDS (American European Consensus definition). Prospective daily data collection was undertaken locally and validated by our research nurse. The influence of the covariates was explored using univariate and multivariate logistic regression.

Patients (375) were diagnosed with ARDS in the 8-month study period. The incidence of ARDS in the ICU population was 8.1%. ICU mortality among ARDS patients was 53.1% (95% confidence intervals (CI) 43–58.2%), dramatically higher than the overall Scottish ICU death rate of 19.3%. Mean APACHE II was 21.9 (CI 21.2–22.7), significantly higher than the mean for the whole Scottish ICU population of 19.3. Univariate analysis found that significant factors associated with death in ICU were age (odds ratio (OR) increasing by 15% for every 5 yr increase in age), APACHE II score (each unit increase increasing OR by 9%), SAPS II score (each unit increase increasing OR by 6%). Admission from ICU/HDU or from a ward doubled the odds of death compared with admission from theatre. Admission variables, which increased OR were systolic arterial pressure (SBP) less than 90 mm Hg (OR 2.53), cardiac dysrhythmia (OR 2.42), acute renal failure (OR 3.93), and immunosuppression (OR 3.24). Length of ICU stay was strongly negatively predictive of death—89% of those with an ICU stay ≤5 days died (OR 11.8). Each day spent in hospital before admission to the ICU increased the OR by 4%. Multivariately, age, SAPS II, SBP <90 mm Hg, days in ICU and days in hospital before ICU are all jointly predictive of death. Extrapulmonary origin of lung injury did not significantly alter mortality.

In an unselected, general ICU population, whose overall outcome is comparable with published series (SMR=0.95), the mortality from ARDS is substantially higher than that reported in some individual series which claim recent improvement in ARDS outcome.[1] Further study into the process of intensive care is required to explain the apparently selective poor mortality from ARDS.

Keywords: complications, acute respiratory distress syndrome

Funding: The Clinical Resource and Audit group, Scottish Office; Astra Zeneca.

References

1 Jardin F, Fellahi J-L, Beauchet A, Vieillard-Baron A, Loubieres Y, Page B. *Intensive Care Med* 1999; **25**: 936–41
2 Rouple E, Lepage E, Wysocki M, et al. *Intensive Care Med* 1999; **25**: 920–9

Intensive Care Society sedation procedure with morphine and midazolam as sedative agents reduces drug budget in intensive care without altering patient outcome

J. Onslow, M. Watters, S. McLeod and A. Pickworth

Princess Margaret Hospital, Okus Road, Swindon SN1 4JU, UK

Many patients admitted to an intensive care unit (ICU) need sedation to optimize care, particularly when mechanically ventilated. Lighter planes of sedation are used in ICU nowadays because newer modes of ventilation allow it and because the adverse effects of over-sedation are widely recognized.[1] Propofol is often used for sedation in ICU, but it is relatively expensive and its superiority over other sedatives in this context is not proven. There is some evidence that cheaper alternatives, such as benzodiazepines can be used successfully in ICU patients along with a sedation procedure.[2]

From 1 April 1999, we have introduced in our ICU a modified Intensive Care Society sedation procedure[3] for patients requiring mechanical ventilation, using morphine and midazolam as first line sedative therapy. Propofol is only used when there is felt to be a specific clinical need. Before 1 April 1999, the ICU used no sedation guidelines. We identified all patients requiring mechanical ventilation for more than 4 h. We reviewed outcome data in these patients over the 2 yr covering the implementation of the procedure. Also, we identified unit spending for sedative medication over the same time. The results are summarized in Table 1. Parametric data were compared with Student's *t*-test, non-parametric data with the chi-squared test. A $P<0.05$ was considered statistically significant; ns=not significant.

Table 1 Patient details and spending on sedation before and after the introduction of sedation guidelines.

	1 April 1998 to 31 March 1999	**1 April 1999 to 31 March 2000**	***P* value**
Patients ventilated >4 h	*n*=231	*n*=244	
Median APACHE score (range)	18 (3–54)	20 (3–51)	ns
Mean length of stay (days)	4.8 (6.0)	4.4 (7.6)	ns
ICU mortality	52 (22%)	65 (27%)	ns
In-hospital mortality	83 (36%)	97 (40%)	ns
3-month mortality	91 (39%)	100 (41%)	ns
Annual unit costs for sedative drugs	£33 958	£8807	

The implementation of the sedation procedure has not altered patient outcome or length of stay in ICU. However, annual sedative drug spending has been reduced by 74% largely a result of reduced propofol and alfentanil usage. Although morphine and midazolam may not be a suitable sedative for every ICU patient, the institution of a sedation procedure based on these two drugs as first line therapy results in considerable cost saving without affecting patient outcome in a UK district general hospital ICU setting.

Keywords: intensive care, audit; analgesics opioid, morphine; hypnotics benzodiazepine, midazolam

References

1 Lerch C, Park GR. *Br Med Bull* 1999; **55**: 76–95
2 Devlin JW, Holbrook AM, Fuller HD. *Ann Pharmacother* 1997; **31**: 689–95
3 Intensive Care Society. *Sedation Guidelines* 1999 (http://www.ics.ac.uk)

Outcome of patients who receive renal replacement therapy in the intensive care unit

K. Daly and A. McLuckie, on behalf of the South Thames Comparative Audit Programme

Department of Intensive Care Medicine, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK

Acute renal failure (ARF) occurs in approximately 5% of all hospital admissions and in about 4–7%[1] of all critically ill patients admitted to the intensive care unit (ICU). Despite improvements in medical treatment and techniques for providing renal replacement therapy the mortality rate for patients has remained persistently high at around 46–90%.[2]

A prospective audit of all patients who required renal replacement (RRT) therapy in the South Thames region was carried out over a 6-month period between January 1999 and June 1999. A standard data set characterizing patient case mix, indications for, and method of RRT together with ICU and hospital outcomes was collected.

A total of 307 patients from 24 adult ICUs were included in the audit. Patients with chronic renal failure were excluded. Renal recovery was arbitrarily defined as the patient being independent of dialysis at the time of ICU discharge (Table 2).

The overall ICU and hospital mortality rates for all 307 patients were 51 and 58%, respectively; 154 patients were treated in centres that performed RRT on more than one new patient per week. These 154 patients were statistically significantly older, had a shorter ICU stay, commenced RRT earlier following ICU admission, and had a lower ICU mortality compared with the centres filtering one or less new patients per week.

Keywords: complications, renal failure; intensive care, outcome

Table 2 Data are given as means with 95% confidence intervals and range (for age)

	All patients (n=307)	**Centres performing RRT >one new patient per week (n=154)**	**Centres performing RRT ≤one new patient per week (n=153)**	***P***
Age (mean yr; range)	60.8 (59.0–62.6)	62.8 (60.5–65.1)	58.7 (56.0–61.4)	0.033
Sex (male %)	65	66	64	ns
Patients ventilated (%)	83	82	84	ns
Patients receiving inotropes (%)	78	77	79	ns
Mean day 1 APACHE II	21.8 (20.9–22.6)	21.8 (20.7–23.0)	21.8 (20.6–22.9)	ns
Mean days in the ICU before starting RRT	2.0 (1.6–2.3)	1.4 (1.0–1.7)	2.5 (2.0–3.0)	0.035
Mean length of ICU stay (days)	13.3 (11.9–14.8)	11.7 (9.9–13.6)	14.9 (12.6–17.2)	0.0001
Recovery of renal function (%)	31	36	28	ns
ICU mortality (%)	51	46	58	0.034
Hospital mortality (%)	58	53	63	0.055

References

1 Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. *Am J Med* 1983; **74**: 243–8

2 Gilbertson AA, Smith JM, Mostafa SM. *Intensive Care Med* 1991; **17**: 204–9

Two-year survival of patients referred, but not admitted, to an intensive care unit

I. J. Rechner, S. Rees, J. Kause and G. B. Smith

Department of Intensive Care Medicine, Queen Alexandra Hospital, Portsmouth PO6 3LY, UK

Patients are usually refused admission to an intensive care unit (ICU) because they are either 'too ill' to benefit or physiologically stable (often termed 'too well'). Although previous work suggests that mortality among appropriately referred patients refused ICU admission is higher than that for admitted patients,[1] there are little data regarding those whose condition does not warrant admission.

Data are routinely collected on all patients referred to the Portsmouth ICU and on all cardiac arrests (CA) attended by the ICU team. We performed a 2-yr follow-up of all patients not admitted to ICU during the period April to September 1997, using ICU referral forms, patient case notes and hospital records. Patient characteristics (age, gender), survival to hospital discharge (HD), and 1- and 2-yr post-referral/CA outcome were recorded, as well as do-not-resuscitate (DNR) status after ICU 'refusal'. Patients were classed as 'too ill' or 'too well' to benefit from ICU admission. No patient was refused ICU admission because of lack of ICU resources; no 'refused' patient was admitted to an alternative high care area. Research ethics committee approval was sought, but considered unnecessary.

During the study period, 245/500 referrals (49%) (216 patients) did not result in ICU admission. Median age of refused patients was 59 yr (14 patients were aged <16 yr); 50% were male. Forty-five patients suffering a CA were unsuccessfully resuscitated and excluded. Of the 22 survivors of a CA, seven were deemed to be 'too ill' and 15 'too well' for subsequent ICU admission. Of the 149 patients that did not suffer a CA (No CA), 40 were classified as 'too ill' and 109 as 'too well'. After ICU refusal, 30 patients were given a DNR status (three were classed as 'too well') (Table 3).

Survival in the CA group was 68, 63, and 63% at hospital discharge, 1 and 2 yr after referral, respectively. However, no patient in the CA group who was deemed to be 'too ill' for admission was alive at 1 yr. Hospital, 1- and 2-yr survival in the no-CA group were 82, 65 and 61, respectively. For patients deemed 'too ill' to benefit from ICU admission, survival at hospital discharge, 1 and 2 yr were 34, 6 and 6%, respectively. In the 'too well' group, survival was 98 (hospital discharge), 87 (1 yr), and 82% (2 yr).

The findings suggest, but do not prove, that decisions regarding the appropriateness of ICU admission in this group of patients were generally correct. The low survival rate of those deemed 'too ill' supports this, and the number of 13% mortality in those deemed 'too well' compares well with the 47% 1-yr mortality rate reported for ICU patients aged >70 yr.[2]

Keywords: intensive care, audit

References

1 Metcalfe MA, Sloggett A, McPherson K. *Lancet* 1997; **350**: 7–11

2 Djaiani G, Ridley S. *Anaesthesia* 1997; **52**: 1130–6

Circulating endothelial progenitor cells in human sepsis

X. Lu, A. Chishti, B. Fulton, R. Bullock, A. Batchelor, A. Gascoigne, J. I. Gillespie and **S. V. Baudouin**

University Department of Surgical and Reproductive Sciences and the Intensive Care Unit, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK

Widespread vascular damage occurs in human sepsis and endothelial cell (EC) regeneration is likely to be important in recovery from critical illness. Division of mature ECs in the vessel

Table 3 Survival of patients referred for, but refused, ICU admission separated into those that had a cardiac arrest (CA) and those that did not

	Too ill				**Too well**			
	Patient nos	**Alive at HD**	**Alive 1 yr**	**Alive 2 yr**	**Patient nos**	**Alive at HD**	**Alive 1 yr**	**Alive 2 yr**
CA	7	1	0	0	15	14	14	14
No CA	40	15	3	3	109	107	94	88

wall has traditionally been viewed as the mechanism responsible for repair. Recently evidence of an alternate mechanism involving immature circulating mononuclear cells, so called endothelial progenitor cells (EPC), has been produced.[1] In this scheme, circulating EPCs are released from the bone marrow and recruited to areas of vascular damage where they differentiate to mature ECs. We have previously reported an increase in the number of circulating mononuclear cells expressing one of the receptors for the vascular endothelial growth factor (VEGF-R2), in human sepsis.[2] EPCs have been identified on the basis of the surface expression of VEGF-R2, AC133, and CD34. We therefore, hypothesized that septic patients may have a population of circulating EPCs.

Initial experiments (n=10) were performed using human umbilical cord blood cells, which are known to contain a high percentage of haematological stem cells. Mononuclear cells were prepared and populations of AC133$^+$ and CD34$^+$ cells subsequently obtained by magnetic bead separation (conjugated MACS beads, Miltenyi Bitoec). Cells were then cultured in medium that included VEGF and stem cell growth factor. Initially cells with a number of different morphologies were observed including small, round cells and spindle shaped cells. After 14–21 days of culture, cells with the morphological, surface staining (to vWf and PECAM-1) and RNA content (by RT-PCR to vWf) of mature ECs were observed. Mononuclear cells were then obtained from three patients with sepsis and AC133$^+$ and CD34$^+$ cells separated. Culture of these cells subsequently yielded populations of mature ECs, similar to those identified previously in the cord blood samples.

Critically ill patients have populations of circulating immature mononuclear cells that can differentiate, *in vitro*, to mature ECs.

Keywords: blood, endothelial cells, regeneration

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References

1 Asahara T, Murohara T, Sullivan A, *et al. Science* 1997; **275**: 964–7
2 Mutunga M, Fulton B, Bullock R, *et al. Br J Anaesth* 2000; **84**: 665P

Neutrophil CXC chemokine receptor expression in sepsis

A. Chishti, J. Kirby and S. V. Baudouin

Department of Anaesthesia, Royal Victoria Infirmary, Newcastle upon Tyne NE3 4LP, UK

Understanding the molecular mechanisms responsible for neutrophil (PMN) recruitment and activation during sepsis, are central in developing strategies to limit the adverse effects of inflammation. The chemokine interleukin-8 (IL-8) is a potent and specific chemoattractant and activator of neutrophils. Two high-affinity receptors, CXCR1 and CXCR2, mediate the IL-8 signal in PMN. We investigated the expression and function of CXCR1, CXCR2 and CD11b the β_2-integrin essential in neutrophil migration and a marker of neutrophil activation, in patients suffering from severe sepsis.

Fifteen patients in the intensive care unit (ICU) of the Royal Victoria Infirmary were prospectively identified as having sepsis syndrome according to internationally agreed definitions.[1] All subjects were enrolled within 24 h of the onset of developing sepsis syndrome. Eight patients admitted to the ICU with diagnoses other than sepsis acted as 'ICU' controls whilst eight volunteers served as healthy controls. Blood samples were collected from each subject every 24 h for 5 days. Receptor expression was determined by immunofluorescent flow cytometry. Plasma levels of IL-8 were measured by an enzyme linked immunosorbent assay technique. Neutrophil chemotaxis against IL-8 was assessed on day 1 for six subjects in each group using 5-μm pore chemotaxis chambers.

Mortality was 40% in the sepsis group, no ICU control patients died. High levels of IL-8 levels were found in both ICU groups, which subsequently decreased over 5 days in both the septic (497.4 pg ml^{-1}, day 1 to 137.1 pg ml^{-1}, day 5, P=0.001) and ICU control groups (21.2–6.2 pg ml^{-1}, P<0.0001). No detectable IL-8 was observed in healthy subjects. IL-8 levels in the sepsis group were significantly elevated compared with the ICU group (P<0.0001); levels were between 9 and 24 times higher. Neutrophil expression of CXCR1 was not significantly different in any group; receptor expression remaining constant throughout the study. PMN CXCR2 expression during sepsis was significantly reduced compared to healthy controls (P=0.0004) but compared with the ICU group CXCR2 expression was only significantly depressed on day 1 (P=0.002). CXCR2 expression in the control groups was not significantly different (P=0.5). In both ICU groups CD11b expression was elevated compared with healthy controls (P<0.0001 and P=0.002, respectively). Septic patients had significantly higher PMN CD11b expression than PMNs in ICU controls (P=0.0001). PMN chemotaxis was reduced in the sepsis group compared with the ICU (P=0.004) and healthy control groups (P<0.02).

A reduced CXCR2 expression in sepsis corresponded to a decreased chemotaxis, which may be significant in terms of immunosuppression in critical illness and a target for receptor antagonists. CXCR1 expression remains unchanged in all groups and this may reflect receptor redundancy in neutrophils.

Keywords: complications, sepsis

Funding: *British Journal of Anaesthesia.*

References

1 Bone RC, Balk FB, Cerra RP, *et al. Chest* 1992; **101**: 1644–55

Blocking integrin function with RGD peptides delays the clearance of macrophages from a murine model of peritonitis

P. Xu, G. Laurent and **G. Bellingan**

Bloomsbury Institute of Intensive Care and Centre for Respiratory Research, Rayne Institute, London WC1E 6JJ, UK

The successful resolution of inflammation requires the clearance of leukocytes. Neutrophils undergo apoptosis and are phagocytosed by macrophages. Macrophages, however, do not die at the inflamed site but emigrate to the draining lymph nodes. In murine models of peritonitis, we have previously shown that macrophage emigration is tightly regulated. This is because clearance of inflammatory macrophages is rapid ($t_{1/2}$ <2 days) compared with resident macrophages ($t_{1/2}$ >14 days). Emigration involves passage through the mesothelial lining and macrophage adhesion to mesothelial cells alters dramatically over the course of inflammation. We thus, hypothesize that macrophage adhesion interactions are a key factor regulating their clearance. Integrins are the most important macrophage adhesion molecules. The small RGD peptide is able to inhibit the function of many integrins including several expressed on macrophages. We examined the ability of RGD peptide to alter macrophage clearance from a murine peritonitis model to determine the importance of integrin function in their clearance.

Table 4 *$P<0.05$ compared with RGES or PBS controls (Student's unpaired *t*-test)

(Doses shown in mg)	**RGD 0.4**	**RGD 0.1**	**RGD 0.04**	**RGES 0.4–0.04**	**PBS**
No. of mice	4	5	5	11	10
Total no. macrophages recovered (mean (SE))	2.68×10^6 (0.69)*	1.84×10^6 (0.58)	1.34×10^6 (0.17)	1.54×10^6 (0.20)	0.98×10^6 (0.15)
No. of PKH-labelled macrophages (mean (SE))	2.49×10^6 (0.72)*	1.81×10^6 (0.49)	1.15×10^6 (0.15)	1.05×10^6 (0.18)	0.46×10^6 (0.06)

Peritonitis was induced in outbred female mice (25–30 g) by the intraperitoneal (i.p.) injection of 4% thioglycollate. This causes peritoneal macrophage numbers to peak on day 5 and to decline to control levels by day 10. Cells in the peritoneum on day 5 (>95% macrophages) were fluorescently labelled by i.p. injection of the dye PKH26-PCL which specifically labels phagocytes. Two hours after labelling mice were injected i.p. with one of three doses of RGD or a non-blocking control RGES peptide, or PBS only. Injections were repeated 24 h later and mice were killed after a further 24 h. Their peritoneal cavities were lavaged and number of total and of PKH-labelled macrophages determined by cell counts, differential counts of stained cytospins and flow cytometry of lavage. To determine if there was any difference in the quantity of macrophages remaining adherent to the peritoneum after lavage imprints of the mesothelial lining of the liver, bowel, spleen, and omentum were viewed for the presence of residual PKH-labelled macrophages. The number of macrophages (total and PKH-labelled) recovered in each group is shown. There was no difference in total or PKH-labelled macrophage recovery between different doses of RGES, which are shown combined (Table 4).

There was no difference in the quantity of PKH-labelled macrophages adherent to the peritoneal surface (blind scoring of imprints by two observers). The significantly greater macrophage recovery from the peritoneal cavity with RGD peptides suggests that blocking integrin function delays macrophage clearance. This is the first demonstration that macrophage clearance from the peritoneum can be specifically inhibited and that clearance from resolving peritonitis may involve an integrin-mediated mechanism.

Keywords: peritoneum; immune response, macrophage

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Elevated bone turnover in hypercalcaemic and normocalcaemic critically ill patients

J. F. Ledson[1], G. R. Masterson[1], S. M. Mostafa[1], N. Gratton[1], E. Manning[2] and W. D. Fraser[2]

[1]Departments of Intensive Care and [2]Clinical Chemistry, Royal Liverpool University Hospital, Liverpool L7 8XP, UK

The pathophysiology of hypercalcaemia in critical illness is poorly understood.[1] Elevated bone turnover resulting from immobilization and hyperparathyroidism has been suggested as an important cause of this condition.[2]

We studied 23 mechanically ventilated, critically ill patients (median age 63 yr, range 27–84 yr) with APACHE II scores >12 who developed hypercalcaemia (plasma adjusted Ca^{2+} >2.6 mmol $litre^{-1}$). For comparison we studied six normocalcaemic, mechanically ventilated patients (median age 53 yr, range 44–70 yr) with APACHE II scores >12. Daily urinary pyridinoline (Pyr), deoxypyridinoline (Dpyr) and plasma carboxyterminal cross-linked telopeptide of type 1 collagen (ICTP) were measured as markers of bone resorption. Plasma carboxyterminal propeptide of type 1 procollagen (P1CP), bone specific alkaline phosphatase (BAP) and osteocalcin were measured as markers of bone formation. Daily plasma parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) were also assayed. Measurements for the hypercalcaemic and normocalcaemic groups were compared using non-parametric methods and statistical significance was assumed when $P<0.05$.

Table 5 Indices of bone resorption and formation (median and range)

	Hypercalcaemics	**Normocalcaemics**	***P* value**
Ca^{2+} mmol $litre^{-1}$	2.58 (2.4–2.9)	2.4 (2.32–2.46)	0.001
Pyr nmol $mmol^{-1}$ creat.	85.42 (31.8–351.6)	142 (55.1–216)	0.69
Dpyr nmol $mmol^{-1}$ creat.	19.27 (8.4–112.7)	22.7 (7.2–31.5)	0.69
ICTP µg $litre^{-1}$	83 (31–178)	85.5 (26.5–139)	0.75
P1CP µg $litre^{-1}$	325 (156–1733)	393.5(165–683)	0.94
BAP unit $litre^{-1}$	17.6 (12.5)	15.65 (11.1–41)	0.71
Osteocalcin µg $litre^{-1}$	4.5 (0.6–12.2)	2.85 (0.85–9.5)	0.11
PTH pmol $litre^{-1}$	2.05 (0.3–17.8)	1.4 (1.1–7.3)	0.46
PTHrP pmol $litre^{-1}$	0 (0–1.3)	0 (0–0.25)	0.16

Medians (ranges) for adjusted Ca^{2+}, indices of bone resorption and formation, PTH and PTHrP in hypercalcaemic and normocalcaemic critically ill patients are presented in Table 5.

These results indicate massive levels of bone resorption and uncoupling of the processes of bone resorption and formation in both hypercalcaemic and normocalcaemic critically ill patients. To our surprise, the increase in bone resorption was similar in hypercalcaemic and normocalcaemic patients. Therefore, increased bone resorption cannot be the sole cause of hypercalcaemia in patients who develop this condition. In the hypercalcaemic group, six patients had secondary hyperparathyroidism, two had immobilization hypercalcaemia with PTH suppression and the remainder had normal PTH levels consistent with either an overlap of these causes, immobilization hypercalcaemia with failed PTH suppression or an, as yet, unidentified cause. All normocalcaemic patients had PTH levels within normal range. Both groups of patients had normal PTHrP levels.

Keywords: complications, elevated bone turnover

References

1 Wolf A, Chuinard R, Riggens R. *Clin Orthoped* 1976; **118**: 124–9
2 Nierman DM, Mechanick JI. *Chest* 1998; **114**: 1122–8

S100β—a marker for septic encephalopathy?

S. A. Leonard, G. Maloney, N. Kelleher, D. Hearney, C. Cody and G. D. Shorten

Department of Anaesthesia, Cork University Hospital, Wilton, Cork, Ireland

The major cause of death in intensive care is the sepsis syndrome, the systemic inflammatory response to infection. Central nervous system (CNS) involvement is manifest as septic encephalopathy, an acute, potentially reversible, disturbance in cerebral function causing confusion, delirium, or coma.[1] [2] It occurs in 70% of patients, correlates with the severity of illness and is associated with a poor prognosis.[3] Monitoring of cerebral function is often rendered impossible by sedation. A potential marker for cerebral involvement is the astroglial protein S100β whose presence in serum is indicative of cerebral damage.[4–6] We hypothesized that severe sepsis is associated with an increase in serum S100β, the magnitude of this increase would correlate with illness severity and be predictive of outcome.

With ethics committee approval and informed consent, patients admitted to the intensive care unit (ICU) with a diagnosis of severe sepsis outside the CNS were recruited. Serum S100β concentrations were measured daily for 5 days. Evidence of infection, severity of encephalopathy, illness severity and organ failure scores, length of ICU and hospital stay and survival were recorded.

Eleven patients have been studied to date (mean (SD) age 55 (15) yr, mean admission APACHE II score=23.3 (7.9)). Serum S100β was abnormally raised in all patients throughout the study period (normal $<0.2\,\mu g$ litre^{-1}, mean admission S100β=0.57 (0.55) μg litre^{-1}, maximum S100β=0.70 (1.64) μg litre^{-1}). Maximum S100β was significantly lower in survivors than non-survivors (0.43 (0.27) μg litre^{-1} (n=8) *vs* 2.88 (2.56) (n=3), respectively, P=0.017). No significant correlation was demonstrable between Serum S100β concentrations and admission APACHE score, Glasgow Coma Score or organ failure score.

Serum S100β concentrations are increased in severe sepsis and extreme levels are predictive of death. S100β is a potentially useful tool in monitoring cerebral function in sepsis.

Keywords: complications, sepsis syndrome; protein, serum S100β .

References

1 Young GB, Bolton CF, Austin TW, *et al. Clin Invest Med* 1990; **13**: 297–304
2 Eidelman LA, Putterman D, Putterman C, Sprung CL. *JAMA* 1996; **275**: 470–3
3 Sprung CL, Peduzzi PN, Shatney CH, *et al. Crit Care Med* 1990; **18**: 801–6
4 Abraha HD, Butterworth RJ, Bath PMW, *et al. Ann Clin Biochem* 1997; **34**: 546–0
5 Rosen H, Rosengren L, Herlitz J, Blomstrand C. *Stroke* 1998; **29**: 473–7
6 Ingebrigtsen T, Romner B. *J Neurosurg* 1996; **85**: 945–8

Central venous catheter tip colonization and insertion location

M. Tivey[1], M. West[2], J. Carr[2], S. J. Coates[1], M. J. Cunningham[1] and P. Allsop[1]

[1]*Department of Intensive Care and* [2]*Department of Microbiology, Queen's Hospital, Burton Hospital NHS Trust, Belvedere Road, Burton-on-Trent, Staffordshire DE13 ORB, UK*

It has been estimated that catheter related blood stream infections have a directly related mortality of up to 25%.[1] Risk of colonization has been shown to vary dependent on the route of insertion. Internal jugular venous catheterization has a reported association with up to three times the risk of tip colonization when compared with the subclavian route.[2–4] Ingress of bacteria from the skin in the relatively mobile neck region has been blamed for this increase in risk.[5] In this study we aimed to establish if the jugular to subclavian risk ratio exists in UK practice, and to investigate the relationship between risk of colonization and the environment at the time of line insertion. Over 6 months we studied 144 of the 185 patients admitted to the intensive care unit (ICU) who either had central venous lines *in situ* or lines inserted on the ICU. A total of 215 central venous catheter (CVC) insertions were recorded, 130 subclavian and 85 internal jugular. In 68 instances (20 jugular, 48 subclavian) lines had to be left in the patient at death for post-mortem purposes. A further 35 lines (16 jugular, 19 subclavian) were not examined because of contamination by the patient or inter-hospital transfer. The remaining 112 lines (49 jugular, 63 subclavian in 86 patients) were subjected to a standardized tip culture using the Maki roll plate technique. The lines were removed when it was felt clinically appropriate by the ICU or ward team. Positive cultures (>10 colonies) were found in 25 (51%) jugular and 19 (30%) subclavian lines (P<0.05, chi-squared) (Table 6).

Table 6 Central venous catheter tip colonization and site of insertion *versus* location

	Insertion location					
	All lines		**Inserted in ICU**		**Inserted outside ICU**	
Line site	***n***	**Positive cultures**	***n***	**Positive cultures**	***n***	**Positive cultures**
Subclavian	63	19	55	18	8	1
Jugular	49	25	18	5	31	20
Total	112	44	73	23	39	21

Of 39 lines (31 (63%) jugular and 8 (13%) subclavian), inserted outside the ICU, 21 (54%) resulted in positive culture, whereas of 73 lines inserted in the ICU only 23(32%) resulted in positive culture (P<0.05). In addition, 20 (65%) of the 31 jugular lines inserted outside ICU resulted in positive culture compared with 5 (28%) of the 18 inserted in ICU (P<0.02). These data suggest that CVC insertion location and anatomical site both play a part in the rate of catheter tip colonization. The internal jugular approach is more commonly used in non-ICU areas and this may be an additional factor in the higher colonization rates of these lines.

Keywords: heart, catheterization; intensive care

References

1 Pittet D. *JAMA* 1994; **272**: 1819–20
2 Collignon PJ, Soni N, Pearson IY, *et al. J Clin Microbiol* 1986; **24**: 532–35
3 Mermel LA, McCormick RD, Springman SR, Maki DG. *Am J Med* 1991; **91** (Suppl 3B): 197–205
4 Norwood S, Wilkins HE, Vallina VL, Fernandez LG, McLarty JW. *Crit Care Med* 2000; **28**: 1376–82
5 Maki DG, Mermel LA. In: Bennett JV, Brachman PS, eds. *Hospital Infections*. Philadelphia: Lippincott-Raven, 1998; 689–724

Source, type, and resistance patterns of nosocomial bacteraemia in a teaching hospital ICU: a 6-month prospective audit

A. Corona[1], P. Wilson[2] and M. Singer[1]

[1]*Bloomsbury Institute of Intensive Care Medicine and* [2]*Department of Microbiology, University College London W1N 8AA, UK*

Our traditional practice for treating bacteraemia is to use short courses of antibiotic monotherapy (Rx), unless otherwise indicated (e.g. endocarditis or osteomyelitis). We investigated the effect of this policy on the incidence of nosocomial bacteraemia, recurrent bacteraemias, fungaemia, and multi-drug resistance in a 6/12 observational prospective study.

The incidence and source of ICU-acquired bacteraemia, recurrences, multi-resistant strains, and fungaemia were recorded in 713 consecutive ICU admissions (455 male, 258 female; 54% medical, median age 62 yr (range 3–96), first 24 h APACHE II score, 16 (range 2–43), ICU stay 4.5 days (range 1–66) and ICU mortality 20.1%). Chi-squared analysis was used to determine significance.

Forty-nine (6.8%) patients developed an ICU-acquired bacteraemia on 60 occasions (10 patients had two and a further patient three episodes). In these patients the APACHE II score of 22 (5–34) was non-significantly higher (P=0.29) although ICU stay at 24 days (range 4–66) was considerably longer (P<0.0001) and ICU mortality higher (44.8%, P<0.02) than in non-bacteraemic patients. The main risk factors were MRSA carriage, renal failure, and surgery (Table 7).

Table 7 Factors governing risk of bacteraemia

	First episode	**Second episode**	**Third episode**
Number of bacteraemias	49	10	1
Time to episode–days; median (range)	7 (3–20)	28 (13–46)	63
Maximum SOFA score median (range)	8 (1–20)	7.5 (0–16)	13
Gram positive infections/ MRSA (%)	19/8 (42%)	9/5 (55%)	1/0 (0%)
Gram negative infections/ multi resistant	23/2 (8.7%)	0	0
Antibiotic Rx – days; median (range)	5 (2–14)	7 (4–21)	not treated

The source of bacteraemia was: i.v. lines (27 patients), GI tract (9), respiratory tract (9), surgical wounds (6), urinary tract (3), and unknown (4). Among Gram positives, the most frequent isolates were coagulase negative *Staphylococcus* (16), *Staphylococcus aureus* (13), and *Enterococcus* spp., (9; 4 being vancomycin-resistant). Among Gram positives, the main micro-organism was *Klebsiella* spp. (14) followed by *Enterobacter* spp. (7); no extended-spectrum β-lactamase producing micro-organisms were found. Polymicrobial growths were obtained on seven occasions. Five patients relapsed with the same micro-organism, all Gram negative: three were line-related and two were a result of ongoing abdominal pathology. There were only two fungaemias, one being polymicrobial. *Candida albicans* was the causative pathogen in one patient admitted post-abdominal surgery and in another having had intra-vasculat line insertion into an infected groin. Seven patients were not treated: four died on the day of the bacteraemia onset, whilst three experienced asymptomatic bacteraemia.

The low rate of multi-drug resistant organisms (especially Gram negatives and fungaemia in long-stay ICU patients), as well as the low rate of relapse, suggests our policy of short duration (5–7 days) antibiotic monotherapy courses is beneficial. Multicentre RCTs are warranted to compare short *vs* long courses, and monotherapy *vs* combination therapy.

Keywords: complications, bacteraemia; intensive care, audit

Pilot of tool for assessing quality of life experienced by survivors of multiple trauma requiring intensive care

S. L. Jones[1], D. O'Daly[2] and S. Sinclair[3]

[1]DCCM Auckland Hospital, Auckland, New Zealand. [2]Heartlands Hospital, Birmingham B9 5SS, UK. [3]University Hospitals Birmingham B29 6JD, UK

Evaluation of successful use of ICU resources has largely centred on mortality. However, this does not account for the impact of quality of life (QOL) experienced by survivors. Measurement of QOL may become an important decision-making tool in the future development of intensive care medicine. Survivors of critical illness may need support structures that address components of their life other than those that relate to the physical illness that necessitated ICU admission in the first place. Trauma patients are young, often with the potential to return to useful function within society. The possible difficulties that they may encounter as a result of critical illness survival need evaluation before strategies for dealing with them can be developed and monitored. Thiagarajan and colleagues found that quality of life decreased significantly after multiple trauma; however, ICU-related morbidity was not specifically considered. Eddlestone and colleagues have uniquely considered this, the earliest time point of assessment was at 3 months after ICU discharge.

We set out to develop a novel, simplified, QOL tool that would enable assessment of patients shortly after discharge from ICU and which could be repeated 3–6 months after discharge.

We adapted a QOL questionnaire from Eddlestone's work that could be applied to patients immediately post-ICU and at a later interval. Trauma patients discharged from Auckland Hospital Critical Care Unit were interviewed whilst within 4 weeks of discharge from the unit. Patients discharged 3–6 months previously were similarly interviewed. Exclusions included associated head injury and pre-morbidity.

This pilot confirms that symptoms relating to critical illness itself are a prominent feature in the early phase of survival from critical illness (Table 8).

Table 8 Symptoms following intensive care

	Recall of ICU (%)	**Hallucination on ICU (%)**	**↑Fatigue (%)**	**↓Ability to concentrate (%)**	**Interrupted sleep (%)**	**Pain (%)**	**Dreams now (%)**
Immediate n=11	63	18	72	45	72	36	9
3–6 months n=14	42	14	50	43	57	50	0

It is possible that because recall of events surrounding ICU stay decline with time, that unless assessment of patients is made in the early discharge period, valuable information relating to assessment of quality of survival may be lost.

Further development of such an assessment tool may contribute to the identification and management of those patients who are going to develop symptoms relating to critical illness survival.

Keywords: complications, trauma; intensive care, audit

References

1 Thiagarajan J, *et al. Anaesthesia* 1994; **49**: 211–8
2 Eddlestone JM, *et al. Crit Care Med* 2000; **28**: 2293–9

Social deprivation and ICU admission in Middlesbrough

S. G. Simms, J. A. Gedney and F. L. Clarke

South Cleveland Hospital, Marton Road, Middlesbrough TS4 3BW, UK

Mortality and morbidity are higher in areas of social deprivation.[1 2] The Townsend Score[1] is an index of material deprivation composed of four variables (unemployment, car ownership, housing tenure, household overcrowding). We looked at ICU admissions over a period of 1 yr to see if areas with high Townsend Scores had a higher rate of ICU admissions, and whether the admission diagnoses were the same in deprived and affluent areas.

Census data from 1991, Townsend Score data, and Standardized Mortality Ratio (SMR) data by electoral ward were obtained from Tees Health Authority. Postcodes given as the main residence of each admission were mapped to this electoral ward data. Of the 525 admissions (ages 2–89 yr) to the 13 general ICU beds across South Tees Acute Trust between January 1999 and December 1999, 159 were from the Middlesbrough area. Re-admissions were excluded. Only patients from areas with the highest and lowest Townsend scores were compared (123 patients). All specialities except transplantation are available on site, so it is likely that the majority of patients from Middlesbrough needing ICU care were included. The most common reasons for admission were gastrointestinal (35 patients), cardiac (30 patients), pneumonia (28 patients), trauma (24 patients), acute renal failure (21 patients), and deliberate self-harm (19 patients). Range of Townsend Scores for the Middlesbrough area are from 8.9 (most deprived) to –6.1 (most affluent). SMR in most deprived area 166; SMR in most affluent area 65 (Table 9).

Table 9 ICU admission rate per 1000 population in two localities with different socio-economic status

Diagnostic group	**ICU admission rates per 1000 population**	
	Townsend Score <–4.0	**Townsend Score >+4.0**
Acute renal failure	0.115	0.160
Gastrointestinal	0.076	0.320
Cardiac	0.115	0.221
Pneumonia	0.076	0.246
Self-harm	0.038	0.185
Trauma	0.076	0.197

There appears to be a difference in ICU admission rates between more affluent and more deprived areas. There is also a difference in the most common admission diagnoses between the two groups.

The need for ICU beds and case mix may be influenced by the 'catchment area' served by the hospital. This may be useful when calculating intensive care bed requirements.

Keywords: intensive care, admission; intensive care, audit

References

1 Phillmore P, Beattie A, Townsend P. *BMJ* 1994; **308**: 1125–8

2 Whitley E, Gunnell D, Dorling D, Davey Smith G. *BMJ* 1999; **319**: 1034–7

Activation of inflammatory cascades during haemodiafiltration using Duraflo® heparin coated circuits

R. Harry, C. Black, P. Langley and J. Wendon

Institute of Liver Studies, Kings College Hospital, Bessemer Road, London SE5 9RS, UK

In patients undergoing cardiopulmonary bypass it has been shown that contact between blood and extracorporeal surfaces results in complement activation and hence in a systemic inflammatory response which can lead to multiple organ failure.[1] Heparin coated circuits (HCC) reduce these detrimental reactions and result in an improved outcome in this setting.[2] The use of HCC's in continuous renal replacement circuits in the intensive care unit has not been studied.

Fifty-six consecutive patients requiring renal replacement therapy on the Liver Intensive Care Unit were randomly assigned to receiving haemodiafiltration using either Duraflo II®, Filtral 12® or Renaflo® circuits with systemic anticoagulation with either heparin or epoprostenol (PGI2). Before haemodiafiltration and after 1, 4 and 12 h of treatment, elastase, tumour necrosis α (TNF α) and interleukin 6 (IL6) were measured as markers of leukocyte and cytokine activation and hence biocompatability. There were no statistically significant differences between the baseline cytokine measurements in the six groups despite a wide variation. The results, therefore, are displayed as percentage change from baseline with interquartile range and compared using Mann–Whitney *U* Test.

Using the Duraflo filter there is a difference in the effect upon biocompatibility dependant upon the anticoagulant used. Table 10 shows the increase in the markers studied when the filter is used with epoprostenol compared with heparin. Statistical significance of $P<0.05$ is shown in Table 10 as *.

Table 10 Activation of inflammation during haemofiltration (mean percentage change and interquartile range)

	TNF		**IL6**		**Elastase**	
	Duraflo+ heparin	**Duraflo+ PGI2**	**Duraflo+ heparin**	**Duraflo+ PGI2**	**Duraflo+ heparin**	**Duraflo+ PGI2**
1	–10 (7)*	9 (15)*	8 (9)*	27 (33)*	–10 (33)	32 (30)
4	–8 (13)*	11 (10)*	0 (18)*	55 (52)*	–2 (42)	42 (26)
12	0 (17)	13 (34)	2 (24)	64 (134)	–15 (32)	20 (20)

Comparing the performance of the Duraflo filter to standard filters, there is no statistically significant difference between the three filters when all are used with heparin with regards to the levels of TNF α or IL6. When epoprostenol is used as systemic anticoagulation, there is an increase in IL6, TNF α and elastase with Duraflo filters above that seen with Filtral and Renaflo. This reaches statistical significance for TNF α and elastase comparing Duraflo with Filtral. The same trend is also seen in the comparison of Duraflo and Renaflo with regard to elastase but does not reach significance at all time points. By 12 h of haemofiltration there is a statistically significant difference between IL6 levels comparing Duraflo with Renaflo and Filtral.

We demonstrate a difference in the effect of the Duraflo haemodialysis filter on biocompatability dependant upon the anticoagulant used that has not been previously reported. Systemic heparin results in better biocompatibility than epoprostenol during the first 12 h of treatment. There is no advantage of Duraflo II over standard filters in the presence of systemic heparin during continuous renal replacement therapy whereas systemic PGI2 may result in reduced biocompatability using Duraflo compared with standard circuitry.

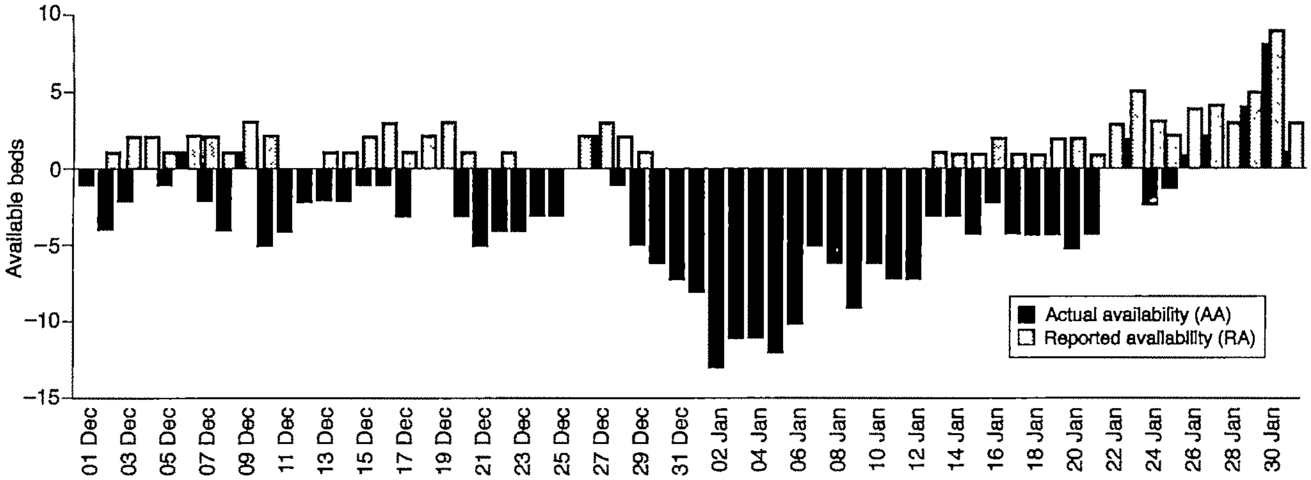

Fig 2 Daily bed availability. On 53/62 days there was excess occupancy. The mean hidden occupancy (RA–AA for each unit) was five beds/day (95% CI 4.32–5.68).

Keywords: blood, anticoagulants; blood, haemofiltration

References

1 Westaby S. *Intensive Care Med* 1987; **13**: 89–95
2 Stammers A, Christensen K, Zavadil D, *et al. J Extra Corpor Technol* 1999; **31**: 135–41

Inaccuracy in reported ICU beds availability—the 'hidden' intensive care

J. Prickett, K. R. Burchett and M. C. Blunt, for the Eastern Area Intensive Care Group (EAICG)

Queen Elizabeth Hospital, Gayton Road, King's Lynn, Norfolk PE30 4ET, UK

The lack of availability of intensive care unit (ICU) beds has been a major problem over recent winters. This excessive requirement has led to many inter-unit transfers, often over long distances, resulting in potentially poor outcomes and intense media interest.[1] The ICU bed register, set up in 1996, monitors the number and location of unused ICU beds, and facilitates transfers. Each unit is telephoned three times a day, and asked to declare free ICU beds. A unit without free beds is noted as full, however, many units were avoiding the increased mortality associated with inter-unit transfer[2] by opening unfunded beds or treating patients in post-anaesthesia care units, coronary care units or elsewhere. The register did not identify this 'hidden' intensive care. The EAICG investigated the discrepancy between the reported and actual general ICU bed use over the worst period of winter 1999/2000.

A questionnaire was sent to all general ICUs in the Anglian Deanery, asking them to provide daily data on the number of funded beds and the maximum number of patients being treated concurrently. The study period was December 1999 and January 2000. All units returned the questionnaire (100% response). Actual bed availability (AA) for each unit was calculated by subtracting the number of patients treated from the number of funded and open beds. Excess occupancy was, therefore, recorded as negative availability. Reported bed availability (RA) was calculated in the same way; however, in this case excess occupancy was recorded as zero availability (in the way bed register reports were formulated) (Fig. 2).

During the majority of December and January last winter there was a substantial shortfall of ICU beds available in the East Anglian region, the position being even worse than appeared from the official figures. In effect, East Anglia ran an unfunded five-bed unit throughout the period. Units should be asked how many patients they are treating and how many beds they have open in order that an accurate picture of bed availability is obtained.

Keywords: intensive care, audit; intensive care, occupancy

References

1 Laville S. *Consultants Fear Crisis Over NHS Bed Shortage.* Daily Telegraph 29/12/1999
2 *Study of Provision of Intensive Care in England.* Department of Health, Leeds, 1993

Sepsis and multi-organ failure does not affect mitochondrial complex I activity

D. Bowen[1], S. Nath[1], S. Pratt[1], D. Rosser[2], R. Waring[1], P. Gosling[2] and M. Manji[2]

[1]Department of Biosciences, University of Birmingham, Birmingham B15 2TT, UK. [2]Department of Intensive Care, University Hospital Birmingham NHS Trust, Birmingham B15 2TH, UK

There is increasing interest in the study of mitochondrial function in sepsis. Sepsis is characterized by a metabolic (lactic) acidosis despite adequate oxygen delivery to tissues/cells. Cellular respiratory function is altered as shown by a decrease in oxygen consumption in septic cells.[1] This is thought to occur as a result of a metabolic defect in the respiratory transport chain resulting in a decrease in the ability to extract oxygen. The respiratory transport chain is an integral part of the inner membrane, composed of ATP synthase, two mobile electron carriers, and four electron transporting protein complexes, designated complex I–IV. As part of a study to determine the effects of sepsis and multi-organ failure (MOF) on these enzyme complexes, here we report the results of mitochondrial complex I activity.

After LREC approval, platelets from patients identified as suffering from severe sepsis and multiple organ failure were harvested from EDTA blood. The platelets were ruptured by

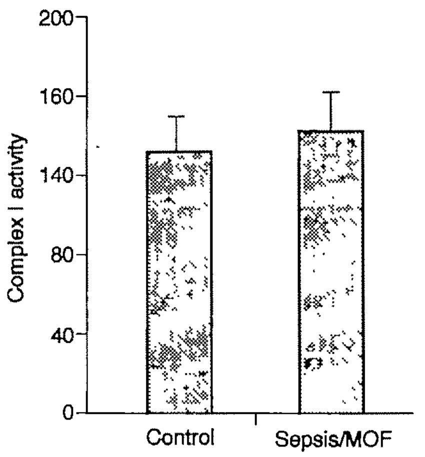

Fig 3 Mitochondrial complex I activity. Data expressed as mean values (nmol NADH oxidized min^{-1} mg protein^{-1}). Error bars represent SEM. Control n=12; sepsis/MOF n=6.

ultrasonication (1.7 A), for 10 s at 4°C to expose the mitochondria. The mitochondrial complex I assay was based upon a previously described method.[2] Rotenone, a known inhibitor of complex I, was used to confirm the specificity of the assay used. Control mitochondria were obtained from healthy volunteers (Fig. 3).

The results show a great variation in individual mitochondrial complex I activities. Although absolute activity values reported here cannot be directly compared with other investigations as assay conditions (temperature, pH, and substrate analogues for ubiquinone) differ considerably, the data obtained was of the same order as previously observed experiments. There is no significant difference in complex I activities of control subjects as compared with patients with sepsis/MOF. This, therefore, suggests that mitochondrial complex I activity is not compromised in severe sepsis and MOF and, therefore, the apparent deficiency in oxidative metabolism must lie in a defect within complexes II–IV of the respiratory transport chain.

Keywords: metabolism, mitochondria; complications, sepsis

References

1 Nath S, Bellingan G, Clutton-Brock T, Manji M, Rosser D. *Br J Anaesth* 1999; **82**: 788P–89P
2 Hatefi Y. In: Fleischer S, Packer L, eds. *Methods of Enzymology*. London: Academic Press, Vol. VIII, 1–14

Septic shock and mitochondrial dysfunction

D. A. Brealey[1], **M. P. Brand**[1], I. P. Hargreaves[2], S. J. R. Heales[2],
J. M. Land[2] and M. Singer[1]

[1]*Bloomsbury Institute of Intensive Care Medicine, University College London W1N 8AA, UK.* [2]*Department of Clinical Biochemistry, Institute of Neurology, London WC1N 3JG, UK*

Mitochondrial dysfunction and respiratory chain inhibition have been described in animal and cell models of sepsis;[1] however, human data are scanty. We hypothesize that associated multi-organ dysfunction is a result of bioenergetic failure. We have previously found that muscle ATP levels are lower in eventual non-survivors of septic shock.[2] We, thus, investigated changes in mitochondrial enzyme activity in patients admitted to intensive care with septic shock.

Muscle biopsies were taken from vastus lateralis within 24 h of ICU admission and at 5-day intervals until death or discharge. Samples were assayed for mitochondrial respiratory chain complexes I, II/III, and IV. Mean enzyme activities are expressed as a ratio to citrate synthase.

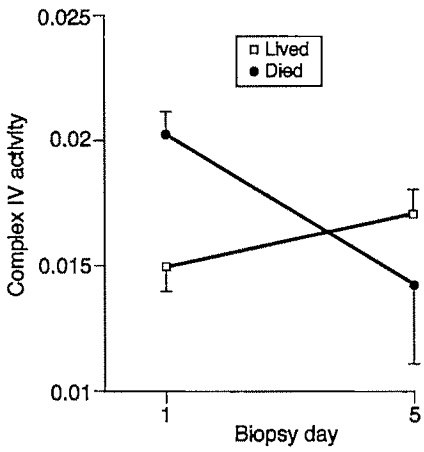

Fig 4 Mitochondrial complex IV activity in muscle from septic patients (mean ± SD).

There were 10 survivors and 11 non-survivors of septic shock, eight and four, respectively, having a second biopsy. No change was seen in complex I or complex II/III activities between survivors and non-survivors; however, complex IV activity showed an increase in those eventually surviving, and a decrease in those dying (ANOVA, P<0.01) (Fig. 4). The Sequential Organ Failure Assessment (SOFA) score fell in survivors (11.5 (1) to 8.8 (1)) but remained unchanged in non-survivors (10.3 (1) *vs* 10.5 (3)) (P<0.08, ANOVA) (Fig. 4).

In conclusion, a statistical difference was found in complex IV activity between patients surviving and dying from septic shock. This may reflect enzyme damage, for example by nitric oxide and peroxynitrite,[3] thus, causing the observed bioenergetic failure. We feel this is an important pathophysiological mechanism that warrants further investigation.

Keywords: metabolism, mitochondria; complications, sepsis

Funding: This work is supported by the Wellcome Trust.

References

1 Brealey DA, Singer M. *Sepsis* 1998; **2**: 291–302
2 Brealey D, Smolenski R, Singer M. *Intensive Care Med* 2000; **26** (Suppl 3): S321
3 Heales SJ, Bolanos JP, Land JM, *et al. Brain Res* 1994; **668**: 243–5

Mitochondrial inhibition is associated with the severity of human septic shock

D. Brealey[1], M. Brand[1], I. Hargreaves[2], S. Heales[2], J. Land[2], N. Davies[3], C. Cooper[3] and M. Singer[1]

[1]*Bloomsbury Institute of Intensive Care Medicine, University College London, London W1N 8AA, UK.* [2]*Clinical Biochemistry, Institute of Neurology, London, UK.* [3]*Biological Sciences, University of Essex, Colchester, UK*

The role of nitric oxide (NO) in the vasodilatation and vascular hyporeactivity associated with septic shock is well established. However, NO and its congenors (e.g. peroxynitrite) have other oxidant effects including inhibition of mitochondrial respiratory chain components, in particular complexes I and IV. This may be an important mechanism causing organ dysfunction.[1] We have demonstrated in cell studies that the antioxidant, reduced glutathione (GSH), protects complex I against NO mediated

Table 11 Correlation coefficients of mitochondrial redox states. C-I=complex I activity, REDOX=complex I redox state, C-IV=complex IV activity

SAPS	C-I	GSH	REDOX	C-IV	
0.25	**0.67**	0.11	0.062	0.05	**NEPI**
	0.10	0.056	**0.72**	0.0	**SAPS**
		0.64	0.25	0.02	**C-I**
			0.214	0.00	**GSH**
				0.56	**REDOX**

inhibition,[2] although this is yet to be demonstrated *in vivo*. We, thus, sought to investigate the link between norepinephrine (NEPI) requirement, activity and redox state (an indicator of function within the respiratory chain) of complex I, complex IV activity, GSH and the severity of illness using the Simplified Acute Physiology Score (SAPS II).

A vastus lateralis muscle biopsy was taken from patients with septic shock within 24 h of ICU admission and frozen immediately at −200°C. The samples were later assayed for (1) complex I and IV (by spectrophotometry), (2) complex I redox state (by electron paramagnetic resonance spectroscopy) and (3) GSH concentration (by HPLC).

Sixteen patients were recruited. Correlation between variables are expressed as r^2 values in Table 11.

This is the first demonstration in patients that the severity of septic shock (as assessed by norepinephrine requirements) is related to decreased mitochondrial activity, in particular complex I. Low complex I activities were also associated with low GSH concentrations. We plan to investigate whether NO levels are raised. Complex IV activity does not relate to clinical status. These results have important implications for the pathogenesis of septic shock and organ dysfunction.

Keywords: metabolism, mitochondria; complication, sepsis

Funding: this work is supported by the Wellcome Trust.

References

1 Singer M, Brealey D. *Biochem Soc Symp* 1999; **66**: 149–66
2 Barker JE Bolanos JP, Land JM, Clark JB, Heales SJ. *Dev Neurosci* 1996; **18**: 391–6

POSTERS

A comparison of four time periods over which to audit the number of high dependency unit (HDU) beds required

J. Low[1 4], J. Nolan[2] and C. Chatfield[3]

[1]Senior House Officer, [2]Consultant in Anaesthesia and Intensive Care, Royal United Hospital NHS Trust, Coombe Park, Bath BA1 3NG, UK. [3]Reader, Department of Mathematical Sciences, University of Bath, Bath BA2 7AY, UK. [4]Present address: Specialist Registrar, Department of Anaesthesia, Milton Keynes General Hospital, Milton Keynes MK6 5LD, UK

Estimating the number of HDU beds needed to meet demand is difficult. Requirement is dependent on the services offered by the hospital and the population that it serves. A snapshot survey, using predefined criteria to identify the number of patients that would benefit from HDU care, provides 'real time' data and, therefore, may be more accurate than retrospective data collection. It is important that a representative time period is used over which to conduct a survey, which is long enough to avoid sampling error caused by the highly variable patient requirement. Various time periods ranging from 2 weeks to 1 month have been suggested,[1 2] but our results suggest that a longer period, of at least 4 weeks is preferable.

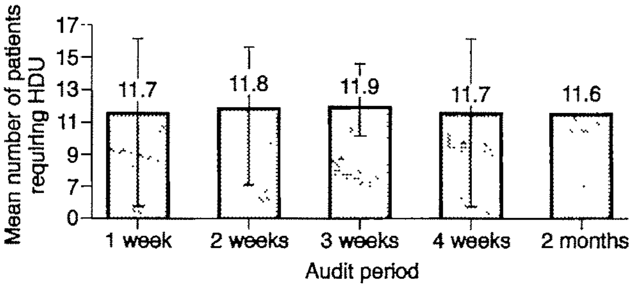

Fig 5 Mean and range of the number of patients assessed as needing HDU using different time periods.

We prospectively audited our need for an HDU over 60 days using criteria published previously.[3] All wards were visited daily and any patient who met the criteria was entered into a database. The data were analysed using discrete time intervals from 1 to 4 weeks and the results were compared with those obtained from the 2-month audit. For example, there were eight 1-week periods and the overall mean for 1-week periods is nearly the same as for the full 60 days (4 days were not used), but the average HDU demand in 1 week varied from a low of 5.6 patients to 16.3 patients. This huge variation shows that a week is too short (Fig. 5).

As may be anticipated, the range increases with a decreasing length of audit. The range varied from 10.7 patients for an audit conducted over 1 week to 3.3 patients when conducted over 4 weeks. We would recommend that the minimum time period used for analysis is 4 weeks, but that 6 or 8 weeks are better. The results will indicate demand at that specific time of year only and, therefore, repeating the audit at different times, for example, high and low demand periods, may allow adjustment for seasonal pressures. Using an empirical approach like this to estimate the number of beds needed may be simpler and more reliable than using complex mathematical models, based on retrospective data.[1]

Keywords: high dependency, audit

References

1 Ridley SA. *Anaesthesia* 1998; **53**: 654–64
2 Meghjee SPL, Wilson RJT. *Br J Anaesth* 2000; **84**: 662P
3 Leeson-Payne CG, Aitkenhead AR. *Anaesthesia* 1995; **50**: 383–7

A survey of the use of epidural analgesia in general intensive care units in England

J. H. S. Low[1 3] and D. Murray[2]

[1]Specialist Registrar in Anaesthetics, Nuffield Department of Anaesthetics, Oxford OX3 9DU, UK. [2]Consultant Anaesthetist, Salisbury District Hospital, Salisbury SP2 8BJ, UK. [3]Present address: Milton Keynes General Hospital, Milton Keynes MK6 5LD, UK

A questionnaire was sent to the named clinical director of all (216) general intensive care units in England. The policies of the unit were sought regarding siting and maintaining epidural catheters in critically ill patients. If the unit had no written policy, then the director was asked to give their opinion. Responses were received from 159 (75%) of units. Eighty-nine per cent use epidurals for analgesia but only 51 (32%) have a written policy covering their use. Anaesthetists or intensivists with an anaesthetic background site all epidurals. The majority of respondents considered positive blood cultures, culture negative sepsis, or evidence of consumptive coagulopathy contraindications to siting an epidural catheter.

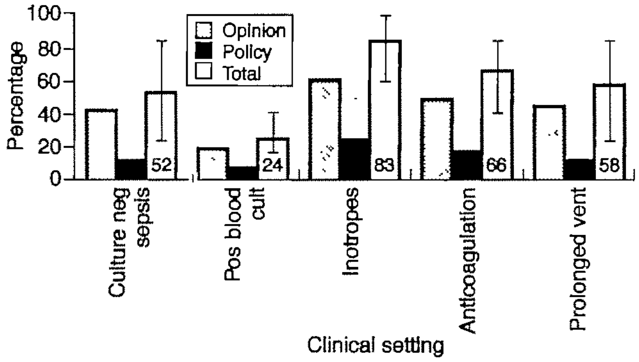

Fig 6 Percentage of units that would maintain an epidural catheter in various clinical settings.

Seventy-one per cent of units would still insert an epidural if a patient required full anticoagulation after it was sited (e.g. haemofiltration). The majority of units (88%) did not seek consent before siting an epidural catheter.

Of the units with a written policy, 42 (81%) do not undertake any microbiological surveillance of epidural catheters while *in situ*. The reported management of epidural catheters when common complications, such as the need for anticoagulation occur is shown in Figure 6. The safety of epidural analgesia in these circumstances has not been established and yet less than 25% of units base these clinical decisions on a written policy. The majority of units felt that epidural catheters should be removed if the blood cultures were positive, but were happy to maintain them in a patient with systemic inflammatory response syndrome (SIRS) provided the cultures remained negative. This paradoxical approach is difficult to justify considering the difficulty in clinically separating these conditions. The majority (66%) felt that full anticoagulation was not a contraindication to maintaining a previously sited epidural.

Many critically ill patients may benefit from epidural analgesia but the presence of one or more contraindications excludes them from receiving this therapy. This survey found marked regional variation in the way units manage epidural analgesia (see Fig. 6 for the range of responses) with the minority having a written policy to guide management in difficult cases. The benefits and risks need to be accurately defined in this group.

Keywords: intensive care, audit; anaesthetic techniques, epidural

Smoking cessation post-critical illness is aided by a self-help rehabilitation programme

C. Jones[1], P. Skirrow[1], R. D. Griffiths[1] and G. Humphris[2]

[1]Intensive Care Unit, Whiston Hospital, Prescot L35 5DR, UK and Department of Medicine, University of Liverpool, Liverpool L69 3GA, UK. [2]Department of Clinical Psychology, University of Liverpool, Liverpool L69 3BX, UK

Smokers make up a high percentage of patients admitted to intensive care (ICU) for community-acquired pneumonia[1] and post-operative complications. Smoking cessation post-ICU has not been examined. However, it should be a high priority to ensure that, as many patients as possible do not return to smoking. The aim of the study was to assess the impact of specific anti-smoking advice given as part of a self-help rehabilitation package on smoking cessation by 6 months post-ICU.

As part of a larger block randomized, controlled trial of a rehabilitation programme patients were asked at 2 weeks post-ICU discharge about their smoking habits pre-ICU admission. At the 8-week and 6-month follow-up clinic appointments, patients were asked whether they had returned to smoking. To verify the patients' assessment a close relative, living in the same house was also asked whether the patient had returned to smoking. The patients received the normal discharge routine, ward visits and ICU clinic plus diaries to record physical recovery and three weekly telephone calls and were then randomly allocated to receive either the rehabilitation package or normal discharge.

Thirty-one intervention and 30 control patients were recruited to the Rehabilitation study. The number of smokers pre-ICU admission was 20/31 intervention patients and 16/30 control patients. Both control and intervention patients were given verbal encouragement to not recommence smoking at three time points, on the ward post-ICU discharge, at the 8-week clinic and the 6-month clinic visit. In addition, the ICU rehabilitation package contained advice on giving up smoking and reinforced the message not to return to smoking. At the 8-week follow-up fewer intervention patients had returned to smoking than in the control group and this was more marked to the 6-month follow-up (see Table 12). The difference was statistically significant at the 6-month point, Fisher's Exact Test chi-squared=7.53, df=1, two-tailed $P=0.006$*.

Table 12 Patients returning to smoking at 8-week and 6-month follow-up

Smokers	Intervention n=31	Control n=30
Pre-ICU admission	20	16
8 weeks	2 (10%)	5 (31%)
6 months	3 (15%)*	10 (62%)*

The anti-smoking advice in the rehabilitation package did have an effect on smoking cessation with 85% of intervention patients, who had been smokers giving up. The health implications of smoking cessation are great. The costs of smoking are wide ranging, not only to the individual and their families through smoking related chronic illness, but to the healthcare services in caring for cancer, cardiovascular and pulmonary disease.[2] In the face of such costs an effective smoking cessation programme is likely to be highly cost-effective.

Keywords: complications, smoking

References

1 Ortqvist A, Sterner G, Nilsson JA. *Scand J Infect Dis* 1985; **17**: 377–86
2 Leistikow BN. *Clin Chest Med* 2000; **21**: 189–97

Factors influencing hallucinatory content in the ICU patient

P. Skirrow[1], C. Jones[1], R. D. Griffiths[1] and S. Kaney[2]

Intensive Care Research Group, [1]Intensive Care Unit, Whiston Hospital, Prescot L35 5DR, UK. [2]Department of Clinical Psychology, University of Liverpool, Liverpool L69 3BX, UK

The negative psychological effects of hallucinatory and delusionary memories from ICU has received increasing attention in recent years.[1] In ICU patients, a number of hallucinatory themes have been identified that may be distortions of either *actual* ICU events or the patient's pre-morbid experiences. In order to investigate this, the present study examined the effects of press coverage of the UN-Serbian conflict in Kosovo on patients' self-reports of hallucinatory content.

Twenty-six patients were followed-up 1–2 weeks after a stay on ICU. All of the patients had been intubated with an ICU stay of ⩾72 h. Patients with burns, head injuries or suicidal behaviour were excluded from this study, as were those with an identified psychiatric history. Of the 26 study patients, 23 (88%) recalled some hallucinatory or delusionary experience from their ICU stay. Patients were questioned as to the content and nature of these experiences, which were recorded verbatim, and these were independently rated for themes of war.

Patients whose ICU stay overlapped with the period of conflict in Kosovo were significantly more likely to remember experiences that involved themes of war (Table 13). Subjects whose stays occurred during the Kosovo conflict did not differ from the other groups on length of stay (P=0.996), illness severity (P=0.789), age (P=0.400) or length of sedation (P=0.455). However, within this group, those patients with hallucinatory themes of war were *significantly older* than those without (P<0.03) and were all of an age that would remember the events leading up to World War II.

The present data are consistent with the findings of studies in other populations[2] that have suggested a strong effect of an individual's past experiences, concerns and expectations on the content of hallucinatory and delusionary experiences. Older patients may have been more concerned by events in Kosovo, fearing they might escalate into a worldwide conflict.

Table 13 Influence of the Balkan conflict on hallucinations after ICU. *P=0.001

Patient group	% Patient experiences with themes of war
Before Kosovan conflict (n=9)	0
During Kosovan conflict (n=7)	43*
After Kosovan conflict (n=10)	0

The identification of alternative explanations for nightmarish memories from ICU is particularly important as it may improve patients' ability to reject them as false, thus, allowing for improved psychological recovery post-ICU.

Keywords: psychological responses, hallucinatory; intensive care, audit

References

1 Jones C, Griffiths RD, Humphris G. *Memory* 2000; **8**: 79–94
2 Baker CA, Morrison AP. *Psych Med* 1998; **28**: 1199–208

Constipation and its implications in the critically ill patient: a national survey of United Kingdom intensive care units

S. M. Mostafa, S. Bhandari, G. Ritchie, E. Arthan and N. Grattan

Intensive Care Unit, Royal Liverpool University Hospital, Liverpool, UK

Gut failure and establishing enteral feeding are recognized and heavily investigated problems in critically ill patients. But scant attention has been given to motility disorders of the large intestine, particularly constipation. A literature search failed to reveal information about constipation or its management in the critically ill. This survey was, therefore, conducted to ascertain whether this problem is common in intensive care units (ICU) in the UK.

A survey questionnaire about constipation was sent to 250 ICUs in the UK. In it, we defined constipation as 'failure of bowel to move'. It included questions about: (1) its incidence and whether it was considered a problem in the corresponding ICU; (2) availability of guidelines for constipation and enteral feeding; (3) its prevention, management and influence on mechanical ventilation (IPPV) and enteral feeding; and (4) unit type, patients age and APACHE II scores.

We received 143 replies (57.2% response rate; 118 (82.5%) from general ICUs, see Table 14). Guidelines for enteral feeding were available in 45.4% (65) of the units. The incidence of constipation was unknown in 45.5% (65) of the units. Whilst 31.4% (45) of the units reported constipation occurring in about 5–20% of their patients 7.7% (11 units) had incidence of >20%.

Table 14 Effects of constipation on outcome from ICU

Constipation	Yes: n (%)	No: n (%)
Is a problem	75 (52.5)	68 (47.5)
Guideline present	5 (3.5)	138 (96.5)
Delays weaning from IPPV	40 (28)	103 (72)
Delays enteral feeding	69 (48.3)	74 (51.7)
Delays discharge from ICU	26 (18.2)	117 (81.8)

The response to the survey was modest. Although more than 50% of respondents confirmed that constipation was a problem in their ICU, only 3.5% had guidelines for the condition. During the survey, we conducted a prospective audit in our ICU. It confirmed the above results. Significantly more constipated than non-constipated patients failed to wean from controlled ventilation (42.5 *vs* 0%, P<0.03).[1] We also found that enteral feeding failed in 27.5% of our constipated patients. Although constipation is not a high priority in the acute phase of treatment of the critically ill, it has the potential of delaying patients' recovery whilst in ICU. The results of this survey raise concern. Further investigation of this problem and its management is warranted.

Keywords: complications, constipation; intensive care, audit

Reference

1 Mostafa S M, Ritchie G. *Intensive Care Med* 2000; **26**: In press

Brain stem death tests and training in intensive care medicine

J. M. Cnpitt and R. J. M. Morgan

Department of Anaesthesia, Blackpool Victoria Hospital, Blackpool, Lancashire FY3 8NR, UK

Brain stem death testing is a fundamentally important clinical tool. Circumstances surrounding performance of the tests are often delicate and sensitive. The most recent Department of Health guidelines[1] state that 'the diagnosis of brain stem death should be made by at least two medical practitioners who have been registered for more than 5 yr and are competent in this field'. The Intercollegiate Board syllabus for intermediate and advanced training in Intensive Care Medicine (ICM) includes familiarity with brain stem death testing as a tick box entry without any requirement for evidence of training or competency.[2] We performed a regional survey to investigate the level of experience amongst trainees in the area of brain stem death testing.

A questionnaire was sent to Specialist Registrars in Anaesthesia with an expressed interest in ICM. The questionnaire asked about personal experience in observing and performing brainstem tests, confidence in performing the tests, and issues relating to discussing tests with relatives. It also enquired regarding the individual's year of training and periods of modular training in ICM.

The response rate for the questionnaire was 38/48 (79%). Thirty-three registrars (87%) felt brain stem testing deserved special emphasis in training. Although the majority of respondents (89%)

felt comfortable with raising the issue of brainstem testing with relatives, only 61% felt confident in performing them. There was wide variation between individuals in the number of tests observed and performed (Table 15). As expected, confidence level increased with year of training but was also dependent on the amount of exposure. In all training years, those that felt confident in performing the tests had observed and performed significantly more.

Table 15 Modular ICM training and trainees experience of brainstem death tests; mean (range)

SpR yr	Intensive care training as SHO (months)	Intensive care training as SpR (months)	No. of tests observed	No. of tests performed
1	4 (3–9)	0	1.5 (0–4)	0
2	2.7 (0–6)	04.6 (3–9)	5.5 (0–18)	0.2 (0–1)
3	3.7 (0–8)	7.7 (6–12)	5.7 (1–14)	1.7 (0–5)
4	2.7 (0–6)	7.9 (3–12)	5.3 (1–10)	2 (0–5)

The 13 intensive care units in the Manchester Deanery approved for SpR training manage a maximum of around 90 brain stem death tests each year (1–2% of admissions). Given the number of Specialist Registrars in the region with an interest in ICM, any individual's exposure to brain stem testing will be limited. The case mix may not be entirely suitable for the learning needs of all trainees and may not be optimal for training. We must ensure that any such deficiencies in gaining the required experience are resolved if our formal training programmes in ICM are to be successful. This will help to ensure the highest standards of patient care.

Keywords: intensive care, audit; education, continuing

References

1 *A Code of Practice for the Diagnosis of Brain Stem Death*. Department of Health, March 1998
2 *Recommendations*. Intercollegiate Committee for Training In Intensive Care Medicine

Prophylaxis against thromboembolism in patients with traumatic brain injury: a survey of UK practice

J. M. Cupitt

Department of Anaesthesia, Hope Hospital, Stott Lane, Salford M6 8HD, UK

Venous thromboembolism is a major complication associated with traumatic brain injury and is responsible for significant morbidity and mortality.[1] There has been general reluctance to use anticoagulant prophylaxis for patients with head injury who have suffered intracranial bleeding or who undergo intracranial surgery. We conducted a postal questionnaire survey of all neurosurgical centres in the UK, enquiring about the use of thromboprophylactic methods in the management of patients with traumatic brain injury.

Twenty-six of the 29 units (90%) used graduated compression stockings whereas only 10 units (34%) used intermittent pneumatic compression (IPC) devices. The latter tended to be used during intraoperative periods only. Of the 17 units (59%) that used heparin, 15 used low molecular weight heparin, one used conventional unfractionated low-dose heparin, and one unit used both types of heparin. One of these units would specifically withhold heparin in patients with diffuse axonal injury, one unit would withhold it only in those with an extracerebral haematoma, and two units would not treat patients with an intracerebral haematoma. Nine units used vena cava filters but rarely as prophylaxis. The time or stage at which heparin therapy was started was very variable amongst the 17 units (Table 16).

Table 16 Neurosurgical units using heparin prophylaxis in brain injury patients

Time/stage at which heparin commenced	Number of units
On admission/post-operative/within 24 h	4
After 72 h	2
After 7 days	5
After 14 days	3
No bleeding apparent	2
Hemiparesis evident	1

A diversity of practice and opinion in the use of such methods was evident from the replies received. The survey highlighted concern about the failure to implement even the most simple means of prophylaxis. Mechanical methods are relatively inexpensive and simple to use with minimal risk. Evidence suggests that the administration of subcutaneous heparin to neurosurgical patients including those with brain injury is a safe and effective method of reducing the incidence of venous thromboembolism without inducing any significant increase of major bleeding.[2] Effective and safe thromboprophylaxis is desirable to prevent venous thrombosis and one should not defer or overlook prophylaxis as a result of undue fear of side-effects.

Keywords: complications, thromboembolism; blood, anticoagulants; brain, injury

References

1 Hammond FM, Meighen MJ. *J Head Trauma Rehabil* 1998; **13**: 36–50
2 Macdonald RL, Amidei C, Lin G, *et al*. *Neurosurgery* 1999; **45**: 245–51

Do you measure tracheal cuff pressure? A survey of clinical practice

C. S. N. Spittle and **S. E. Beavis**

Intensive Care Unit, Hope Hospital, Stott Lane, Salford M6 8HD, UK

It is well recognized that a pressure greater than 30 cm H_2O in the cuff of a tracheal tube can cause mucosal ischaemia and that this may lead to tracheal stenosis or a tracheo-oesophageal fistula.[1] High-volume low-pressure cuffs were introduced in the 1970s in order to prevent these major complications. However, despite their use, there is evidence that tracheal damage still occurs in up to 19% of ventilated critically ill patients.[2] High-volume cuff designs do not guarantee safe cuff pressures as they can easily be over inflated to pressures that will exceed mucosal capillary perfusion pressure.[3, 4] Finger palpation of the pilot balloon has been shown to be unreliable as a method of cuff pressure estimation,[5] and thus, objective measurement of cuff pressure is required to avoid over inflation.

We have surveyed the practice of tracheal cuff pressure measurement in intensive care units (ICUs) in the North West of England. The 32 general ICUs in the region were contacted by telephone and the nurse in charge was asked the following set of questions:

(1) Do you ever measure the pressure in the cuffs of tracheal tubes and tracheostomies on your ICU?
(2) If yes, when do you measure cuff pressure? Regularly/routinely post-intubation or tube change/on admission if

already intubated/only if there is a problem, for example, an air leak?
(3) If regularly, how often?
(4) What is the maximum pressure you will accept in a tracheal tube cuff?
(5) Do you record the cuff pressure on patients' ICU charts?

Thirty ICUs agreed to participate. Thirteen (43%) never measured tracheal cuff pressures and 12 of these did not have any pressure gauges available on their units. Of the 17 (57%) ICUs that measured tracheal cuff pressures only four did so regularly—three measured it every nursing shift and one did so daily. The other 13 ICUs said that they only measured cuff pressures if there was felt to be a problem, for example a suspected leak. Only two (7%) ICUs routinely made measurements after tracheal intubation, a tube change or admission of a patient who was already intubated. Of the senior nurses questioned, 20 (67%) did not know the correct maximum acceptable tracheal cuff pressure. One ICU regularly recorded tracheal cuff pressure on the patient charts and six ICUs occasionally recorded cuff pressures.

This survey indicates that regular measurement of tracheal cuff pressure is unusual and that there is a lack of knowledge about maximum safe pressures in tracheal cuffs. Measurement of tracheal cuff pressure is a quick, simple, and cheap technique. High-cuff pressure is an important and avoidable cause of damage to the tracheal mucosa. We believe that tracheal tube cuff pressures should be measured at least daily and be maintained below 30 cm H_2O.

Keywords: intensive care; equipment, cuff tracheal; complications, tracheal damage

References

1 Lewis FR, Schlobohm RM, Thomas AN. *Am J Surg* 1978; **135**: 452–7
2 Stauffer JL, Olson DE, Petty TL. *Am J Med* 1981; **70**: 65–76
3 Guyton D, Banner MJ, Kirby RR. *Chest* 1991; **100**: 1076–81
4 Seegobin RD, Van Hasselt GL. *BMJ* 1984; **288**: 965–8
5 Fernandez R, Blanch L, Mancebo J, Bonsoms N, Artigas A. *Crit Care Med* 1990; **18**: 1423–6

Clinical experience with the use of sub-anaesthetic doses of halothane in spontaneously ventilating patients with acute severe asthma to avoid ventilation

G. Baigel[1] and **J. Low**[2]

[1]Senior House Officer, Department of Anaesthesia and Intensive Care, Royal Cornwall Hospital, Treliske, Truro TR1 3LJ, UK. [2]Specialist Registrar, Department of Anaesthesia and Intensive Care, Milton Keynes General Hospital, Milton Keynes MK6 5LD, UK

Refractory asthma in ventilated patients has been shown to respond well to inhaled halothane.[1] We used inhaled sub-anaesthetic doses of halothane in five patients with severe, acute asthma, which was refractory to conventional therapy to avoid the need for mechanical ventilation. All five patients were previously diagnosed as having severe asthma and three had required ventilation in the past. After admission to ITU maximal standard asthma treatment was continued and 0.5% inhaled halothane in 100% oxygen alternating with nebulized bronchodilators was added. No patient's required mechanical ventilation and all showed dramatic sustained clinical improvement.

All five patients responded within 10 min. The disappearance of the wheeze was dramatic.

Oxygenation improved in all five patients and only one retained carbon dioxide. All were cardiovascularly stable and were able to communicate throughout the treatment. We initially secured the mask using a Klausens harness, but later stopped doing this and let the patient hold the mask. This allowed a negative feedback loop and prevented over sedation. The average length of time that the patients required the halothane for was 72 min (45–173 min). Four of the patients had one period of therapy but in one patient bronchospasm recurred 10 h after stopping therapy. The patient was aminophylline toxic and had runs of ventricular ectopics when using halothane. When her bronchospasm returned we elected to ventilate her and not to use halothane again. We found that a dose of 0.5% halothane provided the best balance between brochodilation and over sedation. Volatile anaesthetic agents may offer an effective, safe treatment to prevent patients from requiring ventilation for acute asthma (Table 17).

Table 17 Respiratory rate, heart rate, Pa_{O_2}, and Pa_{CO_2} pre- and post-starting halothane therapy

Pre/post-halothane	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
HR (beats min^{-1})	150	128	125	114	131	109	115	112	145	89
RR (bpm)	45	28	24	14	46	29	24	18	32	18
Pa_{O_2} (kPa)	8.6	38	28.8	16.8	12	Not known	8.3	12.8	7.3	24.3
Pa_{CO_2} (kPa)	4.8	5.4	4.3	5.6	8.6	Not known	4.3	5.9	3.3	5.1

Keywords: anaesthetics volatile, halothane; ventilation, spontaneous

Reference

1 Saulnier FF, Durocher AV, Deturck RA, Lefebvre MC, Wattel FE. *Intensive Care Med* 1990; **16**: 104–7

National 1-day survey of haemoglobin in Scottish Intensive Care Units (ICUs)

G. C. **Fletcher**[1] and M. A. Garrioch[2]

[1]Departments of Anaesthesia, Royal Alexandra Hospital, Paisley PA2 9PN, UK. [2]South Glasgow University NHS Trust University of Glasgow, Glasgow, UK. On behalf of the Scottish Intensive Care Transfusion Interest Group

Until recently, haemoglobin (Hb) levels were considered optimal when at or above 100 g litre^{-1}.[1] 'Optimizing' oxygen delivery to tissues by goal directed therapy encouraged the practice of keeping Hb levels high. This practice was recently questioned by the results of the TRICC trial that found that the outcome was improved in certain groups of intensive care patients when their Hb was maintained between 70 and 90 g litre^{-1}.[2] Our intention was to obtain a snapshot of Hb levels and transfusion practice in Scottish intensive care patients. There are 25 ICUs in Scotland. Questionnaires were issued to all ICUs to be completed between 08:00 h, 29 February and 08:00 h, 1 March 2000. All Hb levels measured in this 24 h period were recorded. 24 h APACHE, age, history of ischaemic heart disease, trigger Hb, number of units transfused during the 24-h period and the new Hb level achieved post-transfusion were recorded.

Seventy-six per cent (19/25) of ICUs replied and we surveyed 79 patients. Mean initial Hb level was 102 g litre^{-1} (range 61–153). Mean age was 61.4 yr (range 19–81). Mean (SD) trigger Hb was 86 (9) g litre^{-1}. In 100% of cases, the trigger Hb lay between 70 and 100 g litre^{-1}. Thirteen per cent (10) of patients were transfused on this day. The mean transfusion was 2 (0.6) units. Ischaemic heart disease was present in 29% (n=23) of patients.

Comparing patients with and without ischaemic heart disease, those with no ischaemic heart disease had a lower mean trigger haemoglobin level, but this did not achieve statistical difference (P=0.88) (Fig. 7).

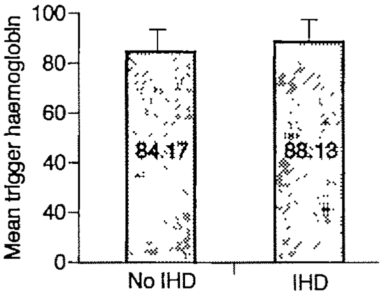

Fig 7 Mean trigger haemoglobin levels (g litre^{-1}) in patients with and without ischaemic heart disease.

Scottish ICUs are transfusing patients with haemoglobin levels between 70 and 100 g litre^{-1} although our trigger haemoglobin for transfusion in many patients still remains higher than that suggested in a recent study.[2]

Keywords: intensive care, audit; blood, haemoglobin

References

1 Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S. *Chest* 1988; **94**: 1176–86
2 Hebert PC, Wells G, Blajchman C, *et al.* *N Engl J Med* 1999; **340**: 409–17

A study of the initial management of patients with elevated intra-cranial pressure: is cerebral perfusion pressure maintained?

I. R. Stanley and D. Hancox

Intensive Care Unit, Royal Preston Hospital, Sharoe Green Lane, Preston PR2 4DU, UK

It is now accepted neurosurgical practice that maintenance of cerebral perfusion pressure (CPP) is an important part of the management of patients with elevated intra-cranial pressure (ICP),[1] and that maintenance of CPP above 70 mm Hg is associated with improved outcome.[2] To maintain CPP it must be possible to measure both mean arterial pressure and ICP. The measurement of arterial pressure is routinely performed on all intensive care units. The measurement of ICP is less easily performed and currently is only available in a few specialist centres.[3] This means that there may be a considerable delay between diagnosis of elevated ICP and the active management of CPP.

Using the ICNARC database all patients who had received ICP monitoring over the previous 21 months were studied. Patients were included if there was an acute onset of pathology, the time of diagnosis of intra-cranial pathology was documented (time of head CT), and the time that CPP management/measurement was started could be identified. It was also recorded if the patient was from another hospital and if they underwent neurosurgery.

Forty-eight patients were included in the study (30 male, 18 female) (Table 18). Aetiology of intra-cranial pathology was subarachnoid haemorrhage (n=10), traumatic intra-cerebral haematoma (n=20), spontaneous intra-cerebral haematoma (n=5), and diffuse head injury (n=13). Twelve of the 48 patients received neurosurgical intervention during their admission.

Table 18 Results of time to measure ICP / manage CPP and initial CPP when measured

	Mean (SD) time to measure ICP/ manage CPP (h)	**Mean (SD) initial CPP (mm Hg)**	**No. of patients with initial CPP <60 mm Hg**	**No. of patients with initial CPP <70 mm Hg**
Internal patient (n=18)	7.5 (4.5)	65 (22)	8	12
External patient (n=30)	8.6 (4.8)	64 (21)	15	20

The limited availability of ICP monitoring leads to a significant number of patients requiring transfer to specialist centres with considerable delay before an important part of management is started. In some of these patients, there is inadequate maintenance of CPP during this time. This also leads to use of scarce neurosurgical beds, by patients not requiring neurosurgery.

Keywords: brain, intracranial pressure

References

1 Robertson C, Valadka AB, Hannay J, *et al.* *Crit Care Med* 1999; **27**: 2086–95
2 Rosner MJ, Rosner SD, Johnson AH. *J Neurosurg* 1995; **83**: 949–62
3 Matta B, Menon D. *Crit Care Med* 1996; **24**: 1743–8

Clinical and organizational problems in patients transferred from the intensive care unit to other areas within the hospital for diagnostic procedures

P. J. Shirley and S. A. Stott

Department of Anaesthesia and Intensive Care, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK

It is common to transport patients from intensive care facilities to areas of the hospital for ongoing investigation and treatment and it has been noted by others that this can be associated with considerable physiological upset.[1–3]

We report the results of 78 patients transferred within Aberdeen Royal Infirmary (ARI) from the intensive care unit (ICU) to other areas of the hospital for investigation between June 1998 and June 1999. These areas included x-ray, CT scanning suite, MRI and nuclear medicine. An attempt to quantify physiological changes was made by calculating mean arterial pressure (MAP) pre-transport, during transport and on return to ICU.

Medical and nursing staff were asked to complete a form for each patient transferred. An attempt was also made to highlight any problems that had occurred during these transfers in the categories of clinical, equipment, or organizational factors. The grade of the medical attendant and their familiarity with the patient was also recorded, as well as the length of time the patient had been in ICU before transfer. The average length of stay in ICU was 143 h pre-transport. Thirty-three (42%) patients were escorted by a senior house officer, 37 (47%) by a specialist registrar and six (8%) by a consultant; for two patients no grade of escort was recorded. The escort had been introduced to the patient an average of 80 h, pre-transport. There was a significant change in MAP during transport from 83 to 77 mm Hg (P<0.05) and an overall increase in MAP on return to the ICU (MAP 89 mm Hg, $P<0.05$).

In 32 cases (41%), no problems were reported, in 29 (37%) a problem with equipment was highlighted, 18 (23%) had an organizational problem, and 13 (17%) had a perceived clinical problem. Despite having a system in place for the transport of these patients, this frequency of clinical and technical problems was considered to be a cause for concern. These problems may be reduced by the introduction of a pre-transport checklist (by adaptation from the current Intensive Care Society guidelines[4]) and a local system of clinical incident reporting.

Keywords: intensive care, audit

References

1 Manji M, Bion JE. *Intensive Care Med* 1995; **21**: 781–3

2 Waydhas C, Schneck G, Duswald KH. *Intensive Care Med* 1995; **21**: 784–9

3 Szem JW, Hydo LJ, Fischer E, Kapur S, Klemperer J, Barle PS. *Critical Care Med* 1995; **23**: 1660–6

4 Intensive Care Society. 1997

Blood and component use in intensive care

H. Boralessa, **M. Rao**, N. Soni, D. Goldhill, S. Brett, C. Morgan, H. Boralessa, D. Watson and M. Contereras

North Thames Blood Interest Group, London, UK

Guidelines available for the use of blood products do not make any specific recommendations for critically ill patients.[1] The study aimed to determine current transfusion practice in this group.

Transfusion data were collected prospectively in patients admitted to seven intensive care units (ICU) in London from January to October 1999. Descriptive statistics were used to analyse data and a *P* value <0.05 was considered significant.

Complete data were obtained in 1247 patients. The overall mortality was 21.5%. The non-survivors were significantly older and had a higher Acute Physiology And Chronic Health Evaluation (APACHE) II score.

Red cells were the most frequently used blood component given to 53% patients. The indication for transfusion was low haemoglobin (Hb) (74%) and haemorrhage (24%) (Table 19). Mortality in the transfused group was significantly higher (25 *vs* 18%). However, the untransfused patients had significantly lower APACHE II scores and higher mean (SD) Hb levels (10.9 (2) *vs* 8.24 (1.5)).

In the cardiovascular group the transfused and untransfused patients had a similar outcome even though the un-transfused patients had significantly lower APACHE II scores and higher pre-transfusion Hb levels. The ICU stay was significantly longer in those transfused and was not affected by the severity of illness.

Sixteen per cent of patients received platelets. The threshold for transfusion was $<30\times10^9$ per litre in 15%, $30–100\times10^9$ per litre in 70% and $>100\times10^9$ per litre in the remainder. The most common indications were haemorrhage and a low platelet count. The mortality in the transfused patients was significantly higher. The survivors had significantly higher platelet counts.

Table 19 Transfusion thresholds for different blood components in various situations. *Values are mean (SD). **Values are median (interquartile range)

Pre-transfusion threshold	Red cells (Hb g dl^{-1})*	Platelets (count$\times10^9$ litre^{-1})**	FFP (prothrombin time in s)*
Overall	8.5 (1.3)	62.0 (45–89)	22.6 (7.7)
Low value	8.4 (0.9)	53.7 (37–74)	22.6 (8.7)
Haemorrhage	8.8 (1.6)	75.0 (50–108)	22.5 (5.4)
Intervention	–	56.0 (40–81)	24.5 (8.0)

Twenty-seven per cent of patients received fresh frozen plasma (FFP). Haemorrhage and a prolonged prothrombin time were the frequent indications.

Only 13 patients received albumin.

Keywords: blood, transfusion

Reference

1 Hebert PC. *Vox Sang* 2000; **78** (Suppl 2): 167–77

Evaluation of APACHE II data collection in two Leicester Critical Care Units

P. M. J. Pratt

University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK

The audit commission report Critical to Success[1] and the Department of Health document Comprehensive Critical Care[2] states the need to be able to compare mortality across critical care units taking into account severity of illness. Many units including the University Hospitals of Leicester use the Acute Physiology And Chronic Health Evaluation score II (APACHE II).[3] This small audit was part of a larger action research study to evaluate two Leicester hospital Critical Care Units approach and consistencies in the collection of APACHE II data sets and the ability to compare actual and predicted mortality.

Nine sets of patient records were randomly selected. Nine Consultant Intensivists completed an APACHE II score on each set of patient data using the patient notes. The final scores and scores for each physiological parameter were then analysed and compared by each consultant.

All parameters were scored for each patient and by all nine consultants. No single parameter was scored consistently and final scores were also found to have a spread of data by up to 15 points. Figure 8 shows the spread of final total APACHE II scores with median highlighted.

This small study is consistent with the findings of Chen and colleagues[4] and hence the ability to compare mortality both predicted and actual may be limited across the wider NHS critical care community. It is, however, suggested by Chen that the inconsistencies are equally spread across the data set hence comparisons are still valid. If critical care units are to be able to compare outcomes then a consistent tool and approach to its use is necessary to allow clinicians and managers to feel secure in the data they present. A national agreement on choice of data set needs to be considered within the modernization of critical care services.

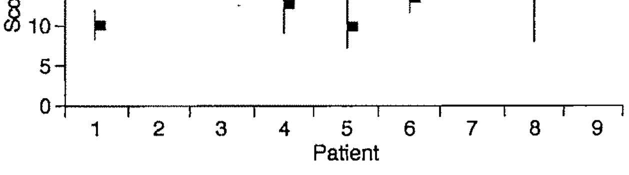

Fig 8 Spread of APACHE scores from individual patients (median and range).

Keywords: intensive care, audit; statistics, APACHE II

References

1 *Critical to Success*. Audit Commission 1999

2 *Comprehensive Critical Care*. Department of Health 2000

3 Knaus WA, Draper EA, Wagner DP, *et al. Critical Care Med* 1985; **13**: 818–29

4 Chen LM, Martin CM, Morrison TL, *et al. Critical Care Med* 1999; **27**: 1999–2004

Sexual dysfunction after intensive care

J. Quinlan[2], M. Gager[1], D. Fawcett[1] and C. Waldmann[1]

[1]*Royal Berkshire and Battle Hospitals, Reading, Berkshire RG1 5AN, UK.*
[2]*The John Radcliffe Hospital, Oxford OX3 9DU, UK*

Subjective quality of life issues are now superceding objective measures of outcome after intensive care. Sexual dysfunction, as part of a full quality of life assessment, has been noted in patients following cardiac surgery[1] and major trauma.[2] Sexual function provides a sensitive measure of outcome in all patients discharged from intensive care but has not previously been specifically investigated.

To assess the incidence of sexual dysfunction we performed a retrospective study of 83 patients attending the intensive care follow-up clinic at the Royal Berkshire Hospital. Patients were asked whether their sex-life had returned to normal. If the answer was no, this was classed as sexual dysfunction.

We then designed a structured questionnaire to investigate the nature of the sexual dysfunction—whether organic or psychological—and to assess the impact of dysfunction on the relationship with their partner. Patients were asked to score their sex life before and after ICU admission and to specify the cause of any change.

In the initial retrospective study, 2 months after discharge from ICU, 30% of patients had sexual dysfunction; at 6 months, 19%; and at 12 months, 12%.

The subsequent prospective study, which is still ongoing, has found that 19 out of 44 patients (43%) experienced sexual dysfunction. Seven patients blamed 'physical changes'; eight felt 'no desire', suggesting a psychological component; one patient's partner and one patient felt frightened that sex might precipitate the admitting illness; while seven patients stated that 'nothing works' despite having the desire, implying a possible organic cause for the dysfunction. Four patients said that sex had improved. Some patients gave more than one cause for their change in sex life, while others gave no reason. Nineteen patients were satisfied with their sex life, despite four having evidence of sexual dysfunction. Fifteen patients were dissatisfied with their sex life; all but two describing sexual dysfunction. Seven patients have been referred for either psychosexual counselling or assessment at an andrology clinic, while two patients have been prescribed sildenafil by their General Practitioner.

Symptoms of sexual dysfunction after major illness are rarely sought by doctors or volunteered by patients. Such problems are common, however, with a significant influence on quality of life, both for the patient and their partner. The intensive care follow-up clinic provides a useful forum for identifying patients with psychological or organic sexual dysfunction, enabling appropriate referral.

Keywords: intensive care, audit; complications, sexual dysfunction

References

1 Nielsen D, Sellgren J, Ricksten S-E. *Crit Care Med* 1997; **25**: 52–7

2 Thiagarajan J, Taylor P, Hogbin E, Ridley S. *Anaesthesia* 1994; **49**: 211–8

Prevalence of *Helicobacter pylori* among intensive care unit nurses

J. J. S. Brown, **A. K. Gregg**, R. M. Powell, A. J. Fox and P. S. Spiers

Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

Helicobacter pylori (HP) is associated with gastritis and peptic ulceration, and implicated in the pathogenesis of gastric carcinoma,[1] coronary heart disease[2] and cerebrovascular disease.[3] The prevalence of HP has been demonstrated to be increased in endoscopists and endoscopy nurses.[4] We assessed the prevalence of HP in 40 nurses working in a busy intensive care unit, compared with 40 matched controls working in a non-clinical clerical area.

We recorded the subjects Glasgow Dyspepsia Severity Score,[5] age, and duration of nursing and intensive care unit (ICU) experience. All subjects were fasted and then given carbon 13 (C^{13})-labelled urea orally. In the presence of Helicobacter, C^{13}-labelled carbon dioxide is produced. A breath test was then used to assess the presence of HP. This is a validated method with very high-test sensitivity and specificify.[6]

There was no difference in the dyspepsia scores or ages of the ICU nurses compared with the non-clinical staff (Mann–Whitney tests, $P>0.05$). The mean duration of nursing experience was 9 yr and ICU experience was 5 yr. There were 6/40 (15%) ICU nurses who tested positive for the presence of HP and 6/40 (15%) non-clinical staff who tested positive for the presence of HP. There was a non-significant trend towards an increased age in the HP positive subjects of both groups, but no increase in dyspepsia score of HP positive subjects, compared with HP negative subjects (Mann–Whitney test, $P>0.05$).

This study suggests that ICU nurses do not have an increased prevalence of HP, when compared with non-clinical staff, despite their very close patient contact.

Keywords: infection, bacterial

Acknowledgements: We would like to acknowledge all the nurses and clerical staff for their participation with the study, and Professor R. Playford for his gastroenterological support.

References

1 Scheiman JM, Cutker AF. *Am J Med* 1999; **106**: 222–6

2 Arbustini E, Morbini P, Bello BD, Prati F, Specchia G. *Am Heart J* 1999; **138**: 55–60

3 Pakodi F, Abel-Salam OM, Debreceni A, Mozsik G. *J Physiol Paris* 2000; **94**: 139–52

4 Goh KL, Parasakthi N, Ong KK. *Am J Gastroenterol* 1996; **91**: 268–70

5 el-Omar EM, Banerjee S, Wirz A, McColl KE. *Eur J Gastroenterol Hepatol* 1996; **8**: 967–71

6 Chen X, Haruma K, Kamada T, *et al. Helicobacter* 2000; **5**: 98–103

Early extubation after oesophagectomy: effect on outcome

D. H. Conway and J. R. Goodall

Department of Anaesthesia and Intensive Care, Hope Hospital, Salford M6 8HD, UK

Surgical resection of oesophageal carcinoma is high risk with a reported mortality of 3–17%.[1] Early extubation has been associated with reduced pulmonary complications.[2] It is intensive care (ICU) policy to extubate patients before ICU admission, utilizing epidural analgesia. The purpose of this study was to assess complications associated with early extubation and compare outcome—length of hospital stay and mortality, with patients intubated on ICU arrival.

The ICU database (PICIS, France) was searched for all patients admitted between January 1998 and 2000, after oesophagectomy. We collated information on patient characteristics, POSSUM scores,[3] physiological parameters during ICU stay and complications. We analysed the data using *t*-test and chi-squared test.

Data from 53 patients were evaluated (eight female, 45 male). Forty-two patients were extubated before ICU admission. Ten of the extubated patients required re-ventilation (all male). Re-ventilation occurred during the initial admission for six patients and after re-admission for four. In total seven patients were re-admitted, five who were extubated before initial ICU admission. Re-admission was associated with increased median length of stay, 16 days (range 5–30) and two deaths, both in men originally arriving intubated. Mortality for patients who remained intubated on initial ICU admission was 45%, which is significantly greater than 4% in those extubated ($P<0.01$ chi-squared test). In patients who arrived intubated, the median pre-operative physiological POSSUM score was 15 (range 14–17), post-operative score 15 (15–23) and predicted mortality 8% (6–20%) (Table 20).

Table 20 Physiological variables and outcome in post-oesophagectomy patients. Values are mean (SD or range)

	n	Age	Lowest pH	Lowest Pa_{O_2} (kPa)	Re-admitted	ICU stay (days)	Died on ICU
Intubated on arrival	11	65 (43–80)	7.27 (0.07)	10.3 (2.27)	2	8 (3–18)	5
Extubated on arrival	42	59 (43–81)	7.30 (0.065)	13.2 (6.5)	5	6.2 (2–30)	2

Early extubation after oesophageal resection may lead to re-intubation being required for some patients. Patients remaining intubated at ICU admission fare very poorly. Further work may determine whether this is a result of selection of potentially complicated cases at the end of surgery or as a result of the effects of post-operative mechanical ventilation.

Keywords: surgery, oesophagectomy; ventilation, intermittent positive pressure

References

1 Begg CB, Cramer LD, Hoskins WJ, Brennan MF. *JAMA* 1998; **25**: 280: 1747–51
2 Caldwell MT, Murphy PG, Page R, Walsh TN, Hennessy TP. *Br J Surg* 1993; **8**: 1537–9
3 Copeland GP, Jones D, Walters M. *Br J Surg* 1991; **78**: 355–60

The effect of neuromuscular block on oxygen consumption in patients with high oxygen requirements undergoing mechanical ventilation

R. Greer[1], W. Russell[1] and N. J. N. Harper[2]

[1]*Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK.*
[2]*Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK*

Neuromuscular blocking agents (NMBA) may be used in intensive care to reduce oxygen demand and improve chest compliance. It has been proposed that neuromuscular block can be used to reduce oxygen consumption by minimizing muscle activity.[1] Use of NMBA can lead to prolonged neuromuscular weakness syndrome.[2] Limiting oxygen consumption by keeping the patient still may equally well be achieved by the use of sedation alone. The aim of this study was to assess the effect of standardized neuromuscular block on patients with a high oxygen requirement.

We investigated 20 patients who required an FI_{O_2} greater than 0.6 to maintain a Pa_{O_2} of greater than 10 kPa. The patients had an indwelling pulmonary artery flotation catheter and arterial line. Sedation was standardized such that the patients demonstrated no movement, no respiratory effort however coughed on bronchial suction. Baseline measurements were made of cardiac output, pulmonary capillary wedge pressure, systemic vascular resistance, arterial oxygen content, arterial saturation, and mixed venous saturation. These were made at time T0. We measured cardiac output by thermodilution and the temperature of the injectate was below 8°C. Oxygen consumption was measured by the reverse Fick method. At time T0, a bolus of atracurium was administered to achieve a standard level of neuromuscular block. We achieved a level of block of one twitch in a train of four. We repeated haemodynamic measurements and calculated the indices of oxygenation at this time, and considered this to be T1. Full spontaneous return of neuromuscular activity was allowed and this was considered to be present when we could elicit no fade on double burst stimulation. Again we calculated oxygen consumption by the reverse Fick method (time T2).

There was a mean decrease in oxygen consumption of 7.7% after neuromuscular block returning to within 2.2% of the baseline after the recovery of muscle function. Statistical significance was not achieved (paired *t*-tests, $P=0.24$–0.92). The measurement error was 10% for calculating oxygen consumption using the reverse Fick method. Eight of the patients achieved changes greater than this; in five patients the consumption decreased and in three it increased.

In conclusion, we have demonstrated that the administration of neuromuscular blocking agents in addition to sedation will not reliably decrease oxygen consumption in patients with a standard level of sedation. Furthermore, in some we have demonstrated that it may increase consumption. We suggest that should this therapeutic option be considered, calculations of oxygen consumption are made after a bolus of atracurium and this may be used as a basis for further management decisions.

Keywords: neuromuscular block, atracurium; intensive care

References

1 Sharpe MD. *Can J Anaesth* 1992; **39**: 949–62
2 Watling SM, Dasta JF. *Crit Care Med* 1994; **22**: 884–93

Outcome of patients who require re-admission to the Intensive Care Unit

K. Daly and A. McLuckie, on behalf of the South Thames Comparative Audit Programme

Department of Intensive Care Medicine, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK

Re-admission to the Intensive Care Unit (ICU) during the same hospital stay is associated with a high mortality, which may be excess of 50%. In response to concerns that patients were being discharged too early because of increasing demand for ICU beds, a prospective audit was undertaken to determine whether the current guidelines on admission to and discharge from ICUs and High Dependency Units (HDUs) were being followed.[1]

The audit was carried out over a 6-month period between January 1999 and June 1999 and included all patients who required re-admission to the ICU within 7 days of discharge.

Eighty-eight patients from 22 adult ICUs in the South Thames Region were included in the audit.

Eleven patients (12.5%) were discharged early because of a lack of ICU beds. The mean length of ward stay before re-admission was 2.2 days. The main reason necessitating ICU re-admission was respiratory failure, because of infection, which accounted for 24% of all cases. Although there was no significant difference between the mean day 1 APACHE II scores for the patient's first and subsequent re-admission, patients had a longer ICU stay on their re-admission. The ICU mortality rate was 25%, whilst hospital mortality was 39%, a further 14% of deaths occurring following ICU discharge (Table 21).

Table 21 Data are given as means with 95% confidence intervals. * Comparison of the first day 1 APACHE II score *vs* the re-admission day 1 APACHE II score. ** Comparison of the first admission length of ICU stay *vs* the re-admission length of ICU stay

		P
Age (mean yr [range])	60.6 [56.9–64.2]	
Sex (% males)	67%	
Mean day 1 APACHE II score (first admission)	18.6 (13.7–23.6)	
Mean ICU length of stay (days: first admission)	5.1 (3.8–6.5)	
Reason for ICU discharge		
Early	12.5%	
Ready	87.5%	
Length of ward stay before ICU re-admission (mean days)	2.2 (1.8–2.6)	
Mean day 1 APACHE II score (re-admission)	16.5 (15.0–18.1)	ns*
Mean ICU length of stay (days: re-admission)	8.7 (6.4–11.0)	0.0011**
ICU mortality	25%	
Hospital mortality	39%	

These results demonstrate that the published guidelines regarding ICU admission/discharge are being followed in the majority of cases.

Keywords: intensive care, re-admission

Reference

1 *Guidelines on admission to and discharge from Intensive Care and High Dependency Units*. London: Department of Health, 1996

Assessment of the seasonal variation in admission rates to intensive care units

M. Garfield[1], S. Ridley[1], A. Kong[2], A. Burns[3], M. Blunt[4] and K. Gunning[5]

[1]Critical Care Complex, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR, UK. [2]Ipswich Hospital, Heath Road, Ipswich IP4 5PD, UK. [3]West Suffolk Hospital, Bury St Edmunds, Suffolk, UK. [4]Queen Elizabeth Hospital, Kings Lynn, Norfolk, UK. [5]Addenbrookes NHS Trust, Cambridge CB2 2QQ, UK

It is commonly perceived by those working in intensive care units (ICUs) that there are seasonal peaks and troughs in admission rates and unit workload. There is also a perception that there is a general trend towards an increase in admissions. To date there has been no attempt to assess the extent of this seasonal variation in unit workload. This study aims to address this issue.

Admission data, including date and time of admission was obtained from five ICUs in the Eastern region. From these data, the number of admissions per month was calculated for each hospital, and divided by the number of beds open during that month, to give a monthly admission rate per bed. A mean admission rate for the region as a whole was then calculated from the individual hospital rates. Statistical time series analysis was performed using Minitab software, using the decomposition function to seasonally adjust the results.

Data representing 16 300 admissions, from April 1992 to January 2000 were obtained from the five units. Statistical analysis showed there to be both trend and seasonal variation in admission rates, with a clear winter peak in admissions, starting in October and peaking in January, followed by a large decrease in early spring. The winter pressures in 1998/1999 seemed to be much more severe than 1999/2000. There also seemed to be a smaller peak in mid-summer, which seems to be getting larger. All five of the units tended to be busy at the same time. Seasonally adjusted admission rates seem to be generally increasing at a rate of 6.45% per year. It is forecast for winter 2000/2001 that the peak admission rate will be 8.2 admissions per bed—busier than 1999/2000, but not as busy as 1998/1999, when there was a peak admission rate of nine admissions per bed. Figure 9 shows a plot of admission rate against month.

Keywords: intensive care, admissions, seasonal variation

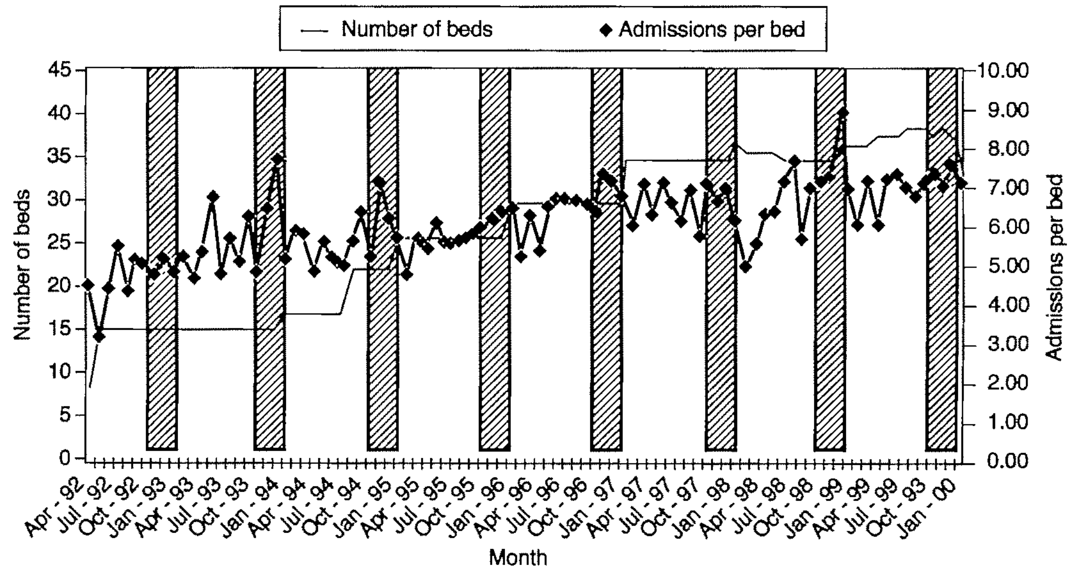

Fig 9 A plot of admission rate against month.

The effect of the zonal retrieval scheme on organ transplant activity

M. J. L. Schuster-Bruce and A. R. Manara

The Intensive Care Unit, Frenchay Hospital, Bristol BS16 1LE, UK

Before 1994 in the UK, all solid organs, except kidneys, were retrieved by the surgical team for transplantation. As this system was both time-consuming and inefficient, a zonal system was introduced in November 1993. Each thoracic and hepatic transplant centre was allocated a geographical zone and became responsible for the retrieval of donor organs within this zone. Each centre was also given the first option on the organs retrieved from its designated area. The introduction of the zonal scheme has been reported to result in widespread benefits including an increase in the number of organs transplanted per donor.[1]

The intensive care unit (ICU) at Frenchay Hospital provides neurosurgical intensive care for a population of 2.5 million, as well as general services for the local population. All solid organ donors from the ICU were identified from the UK Transplant Support Service Authority (UKTSSA) database for the 6 yr before and the 6 yr after the introduction of the zonal system. The number of patients who became solid organ donors and which organs were transplanted in each period were then compared. A total of 135 solid organ donors were identified from whom 704 solid organs were retrieved (Fig. 10). The number of solid organ donors and kidney donors remained unchanged. The numbers of patients from whom livers were retrieved significantly increased (chi-squared P=0.006) in parallel to national figures, whilst there was a significant decrease in the number of patients from whom hearts were retrieved (chi-squared P<0.001).

In the pre-zonal period, the lack of a suitable recipient was the most frequent reason the initial centre offered the heart gave for declining the offer (13 out of 40 offers; 32.5%). Post-zone, concern regarding the medical status of the organ donor was the most frequent reason (26 out of 41 offers; 63.4%). Amongst hearts offered to more than one centre, there was inconsistency in the reasons given for declining the offer. Before the zonal scheme, a rolling rota held by the UKTSSA determined the initial offer centre, subsequently the zonal centre was given first option on 85% of hearts offered for transplantation. The introduction of the zonal scheme resulted in a dramatic decrease in the number of hearts accepted for transplantation. This may be because of different selection criteria amongst cardiac transplant centres.

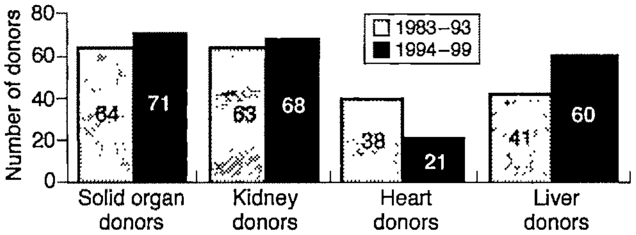

Fig 10 Solid organ donor activity.

Keywords: donors, organ transplantation

Reference

1 *The Report of the Working Party to Review Organ Transplantation*. The Royal College of Surgeons of England, 1999

A randomized trial comparing cisapride and metoclopramide in patients intolerant to enteral nutrition

M. J. L. Schuster-Bruce and A. R. Manara

The Intensive Care Unit, Frenchay Hospital, Bristol BS16 1LE, UK

Impaired tolerance to enteral nitration (EN) is common in the critically ill as a result of delayed gastric emptying (GE). Although cisapride and metoclopramide have both been shown to improve gastric emptying, few studies have been performed in critically ill patients receiving enteral nutrition or those with impaired gastric emptying. Furthermore, comparative studies between prokinetic drugs are lacking in the critically ill.

All patients in our neurosurgical intensive care unit are fed by a strict procedure, which aims to deliver the patient's full energy requirements by 24 h. Ten patients who had been fed for 24 h and who had documented gastroparesis (failure to absorb 50% of their EN requirement in the subsequent 4 h period) were randomized to receive either cisapride 10 mg nasogastric four times daily or metoclopramide 10 mg i.v. three times daily. Gastric emptying was assessed daily by recording the volume of EN infused into the stomach and the nasogastric losses (residual volumes less than 120 ml were returned to the patient). The fraction of EN absorbed [EN input – nasogastric loss]/[EN input] was calculated for the 24-h period before entry on day 0 and for the 24-h period after entry on day 2.

All patients had at least two out of three risk factors for gastroparesis (head injury, narcotics, catecholamines). There was no association between fractional absorption of EN and either intracranial pressure or dose of morphine before entry to the study. Cisapride increased GE in all patients, whereas metoclopramide increased GE in three out of five patients (Fig. 11). The median increase in fractional absorption with cisapride and metoclopramide was 0.74 and 0.38, respectively. This difference did not reach statistical difference. The study is small as it was abandoned prematurely after the Committee on Safety of Medicines advised that all treatment with cisapride should be stopped. However, it may support the suggestion that cisapride is more effective than metoclopramide in the critically ill.[1] Effective alternatives to cisapride are urgently required.

Keywords: complications, gastroparesis

Reference

1 Zolaga GP, Marik P. Promotility agents in the critically ill. *Crit Care Med* 2000; **28**: 2657–9

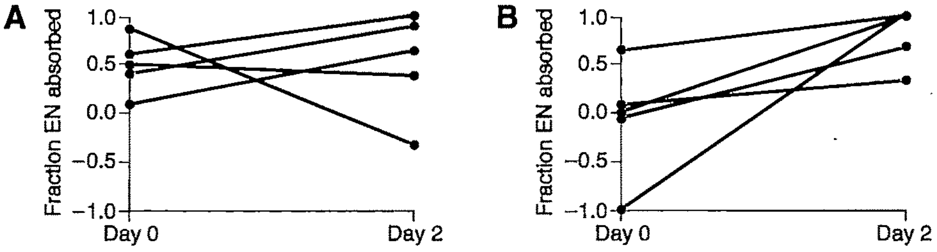

Fig 11 Fraction of enteral nutrition absorbed following either metoclopramide (A) or cisapride (B).

Northern Regional Ventilator Dependency Study—does the northern region need a Regional Weaning Centre?

V. Robson[1], J. Poynter[1], P. Lawler[2] and S. V. Baudouin[1]

[1]*Department of Anaesthesia and Intensive Care Unit, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK.* [2]*Intensive Care Unit, South Cleveland Hospital, Middlesbrough TS4 3BW, UK*

A number of Regional Weaning Centres have been set up in Europe and North America for assessment and treatment of patients who remain ventilator dependent after critical illness.[1–3] These centres provide a successful weaning for 55–70% of such patients,[3] in a less intensive and cheaper environment, and free scarce intensive care beds. This study examines the need for such a weaning centre in the northern region.

A telephone survey of all the 18 intensive care units within the northern region was carried out at 1-week intervals to identify patients who had been ventilated for more than 2 weeks. A series of questions about each patient was asked in order to exclude any patient who would have required intensive care (other than for ventilatory support) during the preceding week, or who was receiving terminal care.

During the initial study period of 70 days, 60 patients were identified as being ventilated for more than 2 weeks. Twenty-six of these, who had only received uncomplicated respiratory support in the previous week, were considered appropriate for a weaning facility. Of the 26 patients, nine were female and 17 were male. The median age was 66.5 yr (range 28–87 yr). Fifteen (55.5%) had undergone surgery immediately before their admission to the intensive care unit. All but one had a tracheostomy. During the study period, 20 of these patients were successfully weaned, one died, and five were still in ICU as a result of ventilator dependence at the end of the study period.

The ventilator-dependent patients occupied ICU beds for a median duration of 7 days (range from 1 to >70 days) after being identified as suitable for a weaning facility. These 26 patients occupied 439 ICU bed-days at hospitals in the northern region, an average of 6.3 beds per day being occupied by patients suitable for a weaning facility. Three patients identified as suitable for a weaning facility at the beginning of the study were still ventilator dependent at the end of the study 70 days later.

Intensive care beds are an expensive and scarce resource. This study has identified a group of patients who currently occupy intensive care beds while needing only ventilatory support, and who could probably be cared for in a lower-intensity Regional Weaning Unit. While the median length of time in the weaning facility would have been 7 days, a small sub-group would have a much longer stay. Other studies have demonstrated the success of such units for carefully selected patients.[1–3] By opening such a unit the northern region could release an average of 6.3 ICU beds each day.

References

1 Elliott MW, Baudouin SV. *Thorax* 1998; **53**: 725–726

2 Scheinhorn DJ, Artinian BM, Catlin JL. *Chest* 1994; **105**: 543–549

3 Scheinhorn DJ, Chao DC, Stearn-Hassenpflug M, LaBree LD, Heltsley DJ. *Chest* 1997; **111**: 1654–9

Keywords: high dependency; ventilation, mechanical

Medical referrals to the intensive care unit: is there enough consultant physician input?

K. D. Rooney[1] and C. Hawksworth[2]

[1]*Department of Anaesthesia and Intensive Care, Crosshouse Hospital, Kilmarnock, Ayrshire KA2 0BE, UK.* [2]*Department of Anaesthesia and Intensive Care, South Glasgow University Hospitals NHS Trust, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF, UK*

Intensive Care Unit (ICU) referrals should be made on a consultant-to-consultant basis.[1] We felt that many medical referrals were not being assessed by the consultant physicians before ICU referral. Therefore, we decided to audit ICU referrals to assess if there was a relationship between referring speciality, grade of referring doctor, and the degree of consultant input before referral.

We undertook a prospective audit of all ICU referrals over a 6-month period at Crosshouse Hospital, a 500-bed district general hospital with a 5-bed ICU. A standardized audit form was completed by the duty anaesthetist for all the patients referred. The completed forms were analysed by the same doctor.

Out of 176 admissions during the same 6-month audit period, 113 forms were completed. The results are shown in Table 22.

Table 22 Referral to the ICU. 'Others' included ENT (4), paediatrics (3), orthopaedics (3), maxillo-facial surgery (3) and obstetrics (3)

Speciality	Medicine	Surgery	A & E	Others	Total
Nos	33	37	27	16	113
Percentage	29	33	24	14	100

In most specialities, consultants made the majority of referrals (median 67%, range 9–100%). However, in general medicine, only three of 33 (9%) referrals came from consultants, most being senior house officer referrals (27 or 82%). A consultant physician had seen only 54% of the medical referrals in the previous 24 h. Overall, 29% of referrals were made without the referring on call consultant being made aware of the referral. Seventy-one per cent of referrals were admitted; of the 29% refused admission, half were not thought to be appropriate referrals by the referring consultant when the case was discussed with them. The on call ICU consultant was aware of 95% of referrals.

Referrals from general medicine account for a significant proportion of ICU referrals, but the vast majority are not referred by consultant physicians and almost a half have not been reviewed by a consultant in the previous 24 h. This suggests that greater consultant involvement by physicians may help reduce ICU referrals. Critical Care Outreach Teams[2] or Early Warning Scoring Systems[2] may help bring these patients to the attention of the consultants earlier and reduce preventable admissions to the ICU.

Keywords: intensive care, medical referrals

References

1 *Guidelines on the Admission and Discharge from Intensive Care and High Dependency.* London: Department of Health, 1996

2 *Comprehensive Critical Care: A Review of Adult Critical Care Services.* London: Department of Health, 2000

Use of multiparameter tissue gas monitoring probes in children with meningococcal sepsis

I. D. Macintosh, S. Nadel, J. Britto and M. Sair

Paediatric Intensive Care Unit, Queen Elizabeth the Queen Mother Wing, St Mary's Hospital, Praed Street, London W2 1NY, UK

Increasing attention is being paid to the assessment of local tissue oxygenation in shock. Several devices aimed at elucidating the state of tissue oxygenation have been used, including tissue microelectrodes. Multiparameter probes conventionally used for intra-arterial measurement represent an accessible and potentially useful technology.

We recruited children who were ventilated with suspected or proven meningococcal disease and evidence of sepsis. A multiparameter tissue probe (Paratrend 7) was inserted sub-cutaneously in the lower limb via a 20-gauge cannula (Arrow). It remained in place, measuring continuously until the child was to be extubated or it ceased working. Simultaneous arterial and venous blood gases were taken from the same limb. Also, cardiac output was measured using a trans-oesophageal probe. Patients were scored for severity on admission using the Paediatric Risk of Mortality Score (PRISM).

Twelve children between the ages of 1 and 7 yr were studied. The probes remained in place for up to 6 days (mean 1.7 days). Mean tissue (t)$P\text{O}_2$ was 7.49 kPa, mean (t)pH was 7.202, mean (t)carbon dioxide was 6.78 kPa and mean oxygen delivery was 514 ml min^{-1}. There was a non-significant trend for tissue $P\text{O}_2$ to vary with oxygen delivery. Patients had PRISM scores of between 5 and 21. There was a trend towards worsening severity scores with worsening tissue pH despite the administration of exogenous bicarbonate (NS). No such trend was seen with simultaneously measured arterial and venous gases. No complications occurred during the period of study. Four sensors failed because they were damaged, usually during patient movement.

Multiparameter tissue probes can be used to monitor subcutaneous tissue gas tensions without complication. Despite the fact that the probes are relatively fragile, with care, it was possible to obtain readings throughout the period in intensive care. Further work needs to be done to establish if there is a consistent and predictable relationship between subcutaneous tissue gases, markers of oxygen delivery and use and severity and outcome.

Keywords: monitoring, subcutaneous tissue gas tensions

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The application of a simple scoring system to audit the changes in practice and success of veno-venous haemofiltration within the intensive care unit of a district general hospital over 3 yr—a comparison of the predictive value of this scoring system with APACHE II

D. V. Pilcher[2], E. Limb[3] and M. Hamer[1]

[1]William Harvey Hospital, Kennington Road, Willesborough, Ashford, Kent TN2 0LZ, UK. [2]St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK. [3]Department of Public Health Sciences, St George's Medical School, London SW17 0RE, UK

A retrospective audit of all patients undergoing haemofiltration at the William Harvey Hospital, Ashford was undertaken covering the period from the beginning of December 1996 to the end of November 1999 to investigate changes in practice and survival.

Biochemical and physiological parameters were collected at initiation of haemofiltration. Each patient's APACHE II score and derived predicted mortality was recorded. Each was also given a 'Haemofiltration Score' derived from a system published by Barton and colleagues in 1993.[1] This was easily calculated from only five variables (age, the need for inotropes, the need for intubation and mechanical ventilation, the urine output and the bilirubin level). These data were then compared with the hospital survival.

There were 15 patients in the first year, 15 in the second and 22 in the third. There was no difference in the APACHE II scores or predicted mortality for the patients in each year but there was an improvement in survival: 20% (3/15) in the first year, 33% (5/15) in the second and 50% (11/22) in the final year. The APACHE II score and predicted mortality did not correlate with survival.

There was a statistically significant reduction in the 'Haemofiltration Score' each year (P=0.005). This correlated well with survival to hospital discharge (P=0.002). A score of 9 or above (range 0–14) was 75.9 sensitive and 76.5% specific for prediction of death. Each year patients were started on haemofiltration who had better predicted outcomes using the 'Haemofiltration Score', despite having similar measures of severity of illness as measured by the APACHE II and predicted mortality. (None of the scores were available to the clinicians managing the patients until after the period of the audit.)

Each year there was a higher number of patients who were not oliguric at initiation of haemofiltration (P=0.02). There was a trend towards a smaller number of patients requiring high dose inotropes (P=0.06). This suggested that haemofiltration was being started 'earlier' in the course of the patients' illness.

This study validated the 'Haemofiltration Score' as a useful tool for prognostic stratification and audit of patients undergoing haemofiltration. Over the 3 yr examined haemofiltration was used more appropriately and there was an improvement in survival.

Keywords: intensive care, audit; statistics, haemofiltration

Reference

1 Barton IK, Hilton PJ, Taub NA, *et al.* *Q J Med* 1993; **86**: 81–90

Cost implications of blood sampling on an intensive care unit

Z. Peto and J. Watts

Burnley General Hospital, Casterton Avenue, Burnley BB10 2PQ, UK

Anecdotal evidence suggests that repeated blood sampling is a cause of anaemia in ICU patients. At the Burnley General Hospital, the intensive care nurses are responsible for ordering routine blood tests, and currently the following tests are performed on each patient on a daily basis: arterial blood gases (ABG), full blood count (FBC), urea and electrolytes (U+E), kidney and liver function, coagulation, bone profile, albumin, globulin and glucose. We examined the clinical and financial consequences of this practice. The effects and cost of blood sampling were determined retrospectively for 20 patients who spent 5 or more days on the ICU between 01/12/1999 to 31/5/2000. A total of 28 patients fulfilled these criteria, but eight patients were excluded as their notes were not available.

The following data were obtained from the clinical records: personal details, diagnosis, days spent on the unit, and total number of each type of blood test performed. We calculated the amount of blood needed for each of the investigations above using the stated filling volume of the sampling tubes and the local ABG practice guideline. Except in the case of the ABG examinations, we compared the number of normal findings to the pathological findings. For the purposes of this study, any blood result, which was outside of the quoted laboratory normal range was classified as 'pathological' even if therapeutic intervention was not required.

The sum total of time spent by the 20 patients on the ICU was 320 days (6–58 days). The total amount of blood taken from the 20 patients being considered was 12 787 ml (257.5–2225 ml). The total cost was £4919.36.

The average amount of blood taken for laboratory investigation was 39.95 ml day patient^{-1}.

The frequency of the blood sampling and the percentage of the pathologic results are shown in Table 23.

Table 23 Frequency of blood sampling and percentage of abnormal results

Sample	ABG	FBC	Coag. profile	U+E kidney	U+E liver, bone protein	Glucose
Average/day	5.03	1.4	0.96	1.82	1.24	1.43
% Pathologic	Not applicable	99.3	21.1	80.1	79.6	37.1

This examination showed that blanket blood sampling was unnecessary, because of the low number of pathological results discovered, and expensive. With careful clinical consideration of every single case, we are able to protect our patients from unwanted blood loss and also reduce cost; not only the cost of analysis, but perhaps also the cost of blood products used. With the help of our results and the cooperation of the nurses, we created a practice guideline of the routine laboratory investigations for our ICU.

Keywords: blood, sampling; intensive care, audit

Underestimation of the anion gap because of hypoalbuminaemia

A. Mayer, S. Skellett, A. Durward, S. M. Tibby and I. A. Murdoch

Department of Paediatric Intensive Care, Guy's Hospital, London SE1 9RT, UK

Clinicians have traditionally equated an increased plasma anion gap (AG) with the presence of tissue metabolic acid (TMA). Figge has shown that hypoalbuminaemia introduces a significant underestimation in the calculated AG.[1] This is likely to be important in an ICU population, where the incidence of hypoalbuminaemia is high.[2] Thus, we may mislabel many acidotic patients as having a 'normal anion gap' resulting in aetiological error and perhaps sub-optimal therapy. TMA may be quantified accurately by calculation of the strong ion gap (SIG) using Stewart's physiochemical theory of acid base.[3] However this is cumbersome and time consuming, and not commonly used in the clinical setting.

We hypothesized that using Figge's formula,[1] the AG corrected for albumin (AG_{corr}) would be a better test than the conventional AG for detecting TMA in the ICU population.

AG, AG_{corr} and SIG were determined from 540 arterial blood samples taken from 341 patients (median weight 8 kg, IQ range 3–15 kg) on admission and at 24 h over a 10 month period on a regional paediatric intensive care unit. The AG (mEq litre^{-1}) was calculated as $([Na^+]+[K^+])-([Cl^-]+[HCO_3^-])$. The AG_{corr} was derived as follows: $AG_{corr}=AG+0.25\times([\text{normal serum albumin}] - [\text{observed albumin}])$ in g dl^{-1}.[1] A normal serum albumin was defined as 44 g litre^{-1},[1] and a raised anion gap was taken as any value >18 mEq litre^{-1} (normal range 16 (2) mEq litre^{-1}).[1] The SIG was calculated using Stewart's strong ion method.[3] The ability of AG and AG_{corr} to quantify TMA was assessed using correlation plots. Incidence of raised AG acidosis before and after correction was compared using the chi-squared test.

In our ICU population, the mean (SD) value for serum albumin was 30 (7) g dl^{-1}. The normal range for serum albumin in well children has been quoted as 33–47 g litre^{-1}.[4] In our population 69% were below this and 15% had extreme hypoalbuminaemia (<20 g litre^{-1}). When an anion gap of 18 mEq litre^{-1} is taken as the upper limit of normal the incidence of a raised anion gap in our population of patients was 26% (143/544) this rose to 53% (286/544, $P<0.0001$) when corrected for hypoalbuminaemia chi-squared $P<0.0001$, Odds ratio 3.1 (95% CI 2.4–4.0). A closer correlation was observed between the corrected anion gap and SIG ($r=0.86$, $P<0.001$), than without correction ($r=0.74$, $P<0.001$). The closer correlation of AG_{corr} with SIG highlights the important quantitative role albumin plays as an anion in plasma.

A significant proportion of raised anion gap metabolic acidosis will be missed in ICU patients without correction for hypoalbuminaemia. The ability of the anion gap to identify tissue metabolic acid is improved by correction of the anion gap for albumin.

Keywords: acid–base equilibrium, metabolic acidosis

References

1 Figge J, Jabor A, Kazda A, Fencl V. *Crit Care Med* 1998; **26**: 1807–10
2 Fencl V, Rossing TH. *Annu Rev Med* 1989; **40**: 17–29
3 Stewart P. *Can J Physiol Pharmacol* 1983; **61**: 1444–61
4 Shann F. *Drug Doses*. Sydney: Collective Pty Ltd, 1996; 69

The use of classification and regression trees to explore and describe the sources of variation in length of stay patients admitted to a high dependency unit

S. Ridley[1], A. Shahani[2] and V. de Senna[2]

[1]Critical Care Complex, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR, UK. [2]Faculty of Mathematical Studies, University of Southampton, Southampton SO17 1BJ, UK

Strategic planning and day-to-day organization of critical care facilities are hampered by the large variations in patients' length of stay. Such variation produces fluctuating workloads and hence unpredictable demands on critical care services. The development of high dependency beds as part of the overall critical care philosophy is being promoted. However, in order to effectively manage a potential group of high dependency patients, it is important that the most influential factors determining their length of stay are identified. Once these are known then the organization, running and development of high dependency services can be more robustly planned. Hence, the aim of this study was to examine the use of classification and regression trees (CART) in determining the most influential factors on length of stay.

Eight hundred and thirty four patients, classified as requiring high dependency care, and admitted to the Critical Care Complex of the Norwich and Norfolk Hospital between 1 April 1999 and 31 March 2000, were studied. A wide selection of patient characteristics available on admission was recorded. These included admission number (first, second, third, etc.), age, sex, time of admission, diagnostic code, referring specialty, emergency or planned admission, surgery or non-operative admission, surgery type (emergency or planned), location of patient before transfer to the Critical Care Complex, APACHE II score, and length of admission. Using length of stay as the dependent variable, the above data was examined using classification and regression tree analysis.

The CART analysis used number of admissions, APACHE score, diagnosis, patient source, and specialty to separate the patients through six layers of divisions to produce 10 terminal groups of patients. These terminal nodes had at least 56 patients and the interquartile range of the patients' length of stay in all terminal nodes except one node did not exceed 2.07 days. This suggests that the variation in the length of stay within the terminal nodes was not excessive and the patients had been divided into sub-groups that were homogeneous with respect to length of stay.

CART analysis may be more useful than other statistical methods such as regression analysis or neural networks because with CART analysis the data are divided into clinically recognizable groups. For example one terminal node contained 100 patients with an APACHE score over 11 admitted for the first time from either another hospital, the general ward or an intensive care bed. This group of patients had a median length of stay 1.72 days with an interquartile range of 0.92–2.99 days. If the present workload of high dependency patients can be divided into such easily identifiable groups, then changes in workload in terms of activity can be predicted and hence managed more efficiently.

Keywords: statistics, classification; statistics, regression trees

Hospital outcome of medical patients following intensive care

M. Trivedi and S. Ridley

Critical Care Complex, Norfolk and Norwich Acute NHS Trust, Brunswick Road, Norwich NR1 3SR, UK

Medical patients suffer a higher mortality, both in the intensive care unit (ICU), and during the remainder of their hospital stay. The survival of medical patients in our institution is poor; the median survival of over 300 medical patients was only 40 days.[1] The causes of post-ICU mortality are unclear. Therefore, aims of this study were to (1) explore possible organizational and clinical influences which affect outcome after ICU and (2) identify categories of medical patients at particularly high risk of mortality.

All patients admitted with a medical cause to ICU and high dependency unit (HDU) of the Norfolk and Norwich Hospital, between 1 February 1999 and 31 January 2000 were studied prospectively. Diagnosis on admission (and discharge, if different) was recorded, and whether the reason for admission was a new clinical problem or an exacerbation of existing chronic illness. Survival on ICU and after discharge from ICU was noted from ICU and hospital records. If the patient died in hospital after discharge from ICU, the cause of death or post-mortem findings were recorded, as was the resuscitation status of the patient.

A total of 190 ICU admissions (186 medical patients) were included in the study. Four patients were readmitted to hospital more than twice (and so counted as separate admissions) while three patients were readmitted from the hospital general ward after discharge from ICU (and so were regarded as the same hospital admission). Fifty-four medical patients died on ICU (28.4% mortality) and a further 16 died on the general ward after ICU discharge (hospital mortality 36.8%). For all patients, mortality was highest in those where the admission diagnosis was not the same as the cause of death (complete agreement between admission diagnosis and cause of death (n=159) 35.8% hospital mortality *vs* no agreement (n=8) 62.5% mortality).

In the 16 patients who died on the general ward, 12 had been admitted to ICU with a new previously unrecognized problem rather than exacerbation of a chronic pre-existing problem. On discharge from ICU, the expected outcome for these patients was to survive and return home. However, on the general ward, 'Do Not Resuscitate' orders were placed on seven of these 12 patients. The total hospital admission for these seven patients before their deaths amounted to 125 days of hospital care.

Medical patients undoubtedly suffer a higher ICU mortality by nature of the underlying pathological process. If this process is not identified, the patients do not do well; this emphasizes the importance of correct diagnosis early in ICU admission. Furthermore, it would appear that some of the high post-ICU hospital mortality may be because of changes in resuscitation status in patients expected to survive after ICU discharge. Some of these changes may have been appropriate but also call into question the value of subjecting these patients to a total of 125 days of hospital care. If these results are confirmed in other institutions, then follow-up by the critical care team becomes even more important.

Keywords: intensive care; complications, death

Reference

1 Lam S, Ridley S. *Anaesthesia* 1999; **54**: 845–52

Initial assessment of the Servo 900C ventilator for use in a hyperbaric chamber

S. Pambakian[1], G. Gardiner[1] and **J. E. Risdall**[2]

Royal Hospital Haslar, Gosport, Hants PO12 2AA, UK. [2]Department of Anesthesiology, University of Texas-Houston Medical School, Houston, TX 77030, USA

Hyperbaric oxygen (HBO) is indicated for a variety of conditions and some of these patients are intubated, ventilated, and receiving intensive support. The acceptability of HBO may be limited by the basic, ventilatory modes available with many in-chamber ventilators. The Servo 900C (Siemen Corp., Denmark), although by no means a 'state of the art' intensive care ventilator, does offer more flexibility, including the application of positive end-expiratory pressure (PEEP) and possibilities of pressure-controlled (PC) and inverse ratio ventilation.

An unmodified Servo 900C was set to ventilate a compression-spring test lung (Datex-Ohmeda, UK) and monitored throughout two Royal Navy Table 66 recompression schedules. It was set to deliver PEEP +5 cm H_2O; PC (above PEEP) +20 cm H_2O; respiratory rate 17 bpm; inspiratory:expiratory ratio 1:2; tidal volume 500 ml during the first run and 400 ml during the second run. The tidal volumes delivered were recorded from both the ventilator and a separate spirometer. Peak inspiratory and end-expiratory pressures were recorded during the second compression. Royal Navy Table 66 was developed for treatment of patients requiring HBO and it limits the depth to 14 m seawater. Descent is typically over 10–15 min, 90 min are spent at depth, and ascent is at a steady rate over 10 min.

Although the Servo 900C performed satisfactorily at depth and during descent, the over-ventilation and loss of PEEP during ascent were unacceptable. For the Servo 900C to be used effectively in a hyperbaric chamber, it will have to be modified such that the tidal volumes delivered are referenced to the ambient pressures, particularly during ascent (Fig. 12).

Keywords: ventilation, hyperbaric chamber

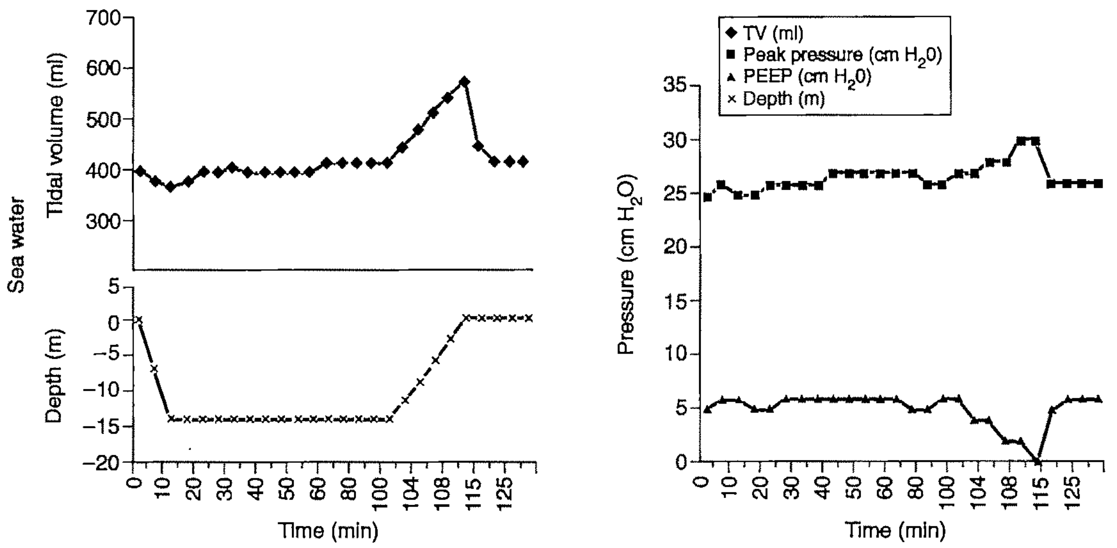

Fig 12 Servo 900C volumes and pressures delivered during RN Table 66.

Sequential organ scoring as a measure of effectiveness of care in the high dependency unit

R. J. De Silva, A. Anderson, H. Tempest and S. Ridley

Critical Care Unit, Norfolk and Norwich Acute NHS Trust, Brunswick Road, Norwich NR1 3SR, UK

The Logistic Organ Dysfunction System (LODS) provides an objective tool for assessing severity levels for organ dysfunction in the critical care unit.[1] This score quantifies dysfunction of the neurological, cardiovascular, renal, respiratory, haematological and hepatic systems and calculates the probability of subsequent hospital mortality. The LODS has been used for measuring effectiveness of treatment and providing a standard of care for patients in an intensive care unit.[2] The aim of our study was to investigate the effect of high dependency care on patients by measuring changes in LODS score over time.

The daily LODS score was calculated for 50 consecutive patients whose stay in the high dependency unit (HDU) of a busy district general hospital exceeded 48 h. There were no deaths. Forty-nine patients were transferred back to the general ward, and one to the intensive care unit. A total of 222 days were spent in the HDU; the patients median length of stay of 4.0 days with a range of 3–21 days. Distribution of the median (and interquartile range (IQR)) daily LODS scores are shown in Figure 13.

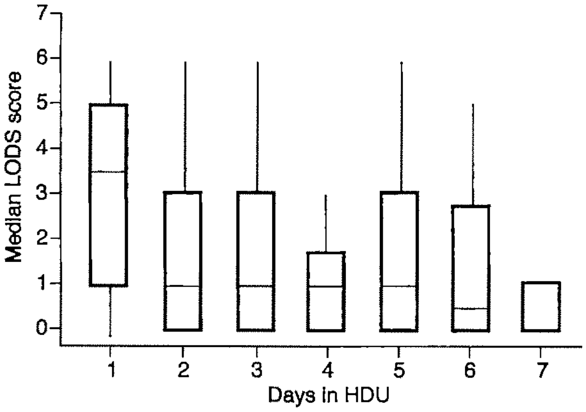

Fig 13 Distribution of the median daily LODS scores. The boxes give the median values (lines across box) and IQR (top and bottom of box) while the whiskers define first quantile −1.5×(IQR) and third quantile +1.5×(IQR).

The median LODS value on admission was 3.5 (IQR 1–5), declining to 1.0 (IQR 0–2) after 72 h of HDU care. Forty-one patients (82%) were discharged to the general ward with a LODS score of 2 or less (median LODS score on last day of HDU care 1 (IQR 0–1).

HDU care reduced the LODS score of patients by over two-thirds and allowed patients to be returned to the general ward with only modest physiological derangement. The LODS score is a useful tool for assessing the effectiveness of high dependency care and establishing standards of physiological derangement compatible with safe discharge to the ward.

Keywords: high dependency; measurement techniques, logistic organ dysfunction system

References

1 Le Gall JR, Klar J, Lemeshow S, *et al.* ICU Scoring Group. *JAMA* 1996; **276**: 802–10
2 Hutchinson C, Craig S, Ridley S. *Anaesthesia* (in press)

Serum magnesium as a predictor of intensive care unit (ICU) mortality

R. A. Walker and G. J. McCarthy

Department of Anaesthesia, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK

Abnormal magnesium levels have been associated with increased mortality in some ICU patients.[1] [2] The aim of this study was to evaluate serum magnesium as a predictor of ICU mortality in comparison to the Acute Physiology and Chronic Health Evaluation (APACHE II) score.

All ICU admissions to a district general hospital over a period of 18 months were reviewed. APACHE II and admission serum magnesium levels between survivors and non-survivors in each group were compared after log transformation of magnesium levels. Stepwise Logistic Regression Analysis was used to assess the contribution of each variable to the prediction of hospital mortality. Then the accuracy of outcome prediction was assessed by using the area under the Receiver Operator Characteristic (ROC) curve.

A total of 588 cases were reviewed. Survivors had lower serum magnesium levels than non-survivors (Table 24). Combining transformed admission serum magnesium levels with APACHE II scores made a small but statistically significant improvement in outcome prediction for hospital mortality over that of APACHE II (*P* value 0.0059). The area under the ROC curve for the APACHE II score alone was 0.81 significantly higher than that for the admission magnesium level (0.64).

Table 24 Average serum magnesium levels. Values represent mean (SD). *Student's *t*-test *P*=0.0004

	Survivor	Non-survivor
Number	457	131
Average serum magnesium (mmol litre^{-1})	0.8 (0.29)	0.93 (0.37)*

These results confirm that there is an association between hospital mortality and admission magnesium levels, but as a single predictor it is inferior to the APACHE II score alone. Nevertheless, in combination with APACHE II, these magnesium levels improved the accuracy of outcome prediction in our dataset.

Keywords: ions, magnesium; intensive care, mortality

References

1 Fawcett WJ, Haxby EJ, Male DA. *Br J Anaesth* 1999; **83**: 302–20
2 Guerin C, Cousin C, Mignot F, Manchon M, Fournier G. *Intensive Care Med* 1996; **22**: 724–7

An audit of the use of intracranial pressure (ICP) monitoring in a district general hospital ICU

J. M. Barker

Intensive Care Unit, North Manchester General Hospital, Delaunays Road, Crumpsall, Manchester M8 5RL, UK

There are few intensive care units in non-neurosurgical centres that insert ICP monitors to aid the management of patients with severe brain injury. We do. The device we use is the Codman Microsensor$^{\text{TM}}$ Skull Bolt Kit, which is simple to insert and placed subdurally. An increasing body of opinion says that cerebral perfusion pressure (CPP) directed therapy might influence outcome[1] in patients with severe head injury. After centralization of neurosurgical services away from North Manchester General Hospital in 1997, ICP monitors are now inserted by the intensivists. I have looked critically at the indications for bolt placement, the time to insertion, the use of data that these monitors provide and the complication rate.

A retrospective audit of 20 case notes was conducted. This represented all the patients on the ICU between 12/2/1999 and 1/6/2000 who had ICP monitors inserted. All were intubated, sedated, and ventilated. Data were collected with regards to: patient characteristics, history, and diagnosis, CT-scan result, time to monitor insertion from ICU admission, value of ICP on insertion, complications, days *in situ*, and whether the data influenced clinical decisions.

All patients had suffered acute brain injury in the form of trauma (55%), subarachnoid haemorrhage (35%) or an intracerebral bleed (10%). None required neurosurgical intervention. Fifteen patients had oedema on their CT-scan, of these eight had raised ICP. Five patients had no oedema on their scan and a normal ICP (there is a documented incidence of raised ICP (13%) in patients whose admission CT is normal).[2] Eleven patients had CPP directed therapy, four had treatment withdrawn and one patient had both. The remaining six had no change in their management. The mean time to monitor insertion was 4–5 h (range 0–23 h). The mean duration of monitor placement was 2.4 days (range 1–6 days). This value was 2.9 days (range 1–6 days) in the subgroup with normal ICP (<15 mm Hg). Therefore, after early bolt insertion, removal was often delayed especially when the ICP was normal. The only complication was a minor scalp haemorrhage.

This is a simple, low risk procedure with a high yield of clinically useful information in the majority of cases. As ICP monitoring/CPP directed therapy is integral to managing brain injury its use should be encouraged in the DGH setting.

Keywords: monitoring, intracranial pressure

References

1 Rosner MJ, Rosner SD, Johnson AH. *J Neurosurg* 1995; **83**: 949–62
2 Narayan RK, Kishore PR, Becker DP, *et al. J Neurosurg* 1982; **56**: 650–9

Trans-laryngeal tracheostomy: modification for a single operator

A. Walder

Intensive Care Unit, North Devon District Hospital, Barnstaple, North Devon EX31 4JB, UK

In a district general hospital, there may only be one experienced intensivist available to perform bedside procedures. Our unit has adjusted the Fantoni technique[1] of trans-laryngeal tracheostomy (TLT) to allow safe insertion by a single-handed intensivist with nursing support.

All patients requiring a tracheostomy as part of their respiratory management underwent TLT using a sterile kit (Mallinkrodt, Mirandola, Italy). After appropriate positioning, sedation and paralysis of the patient, the narrow gauge (4.0 mm) cuffed oral tracheal (ET) tube provided in the kit was first substituted for the patient's normal ET by the operator. The tube was carefully placed distal to the TLT insertion site (to avoid cuff puncture), but proximal to the carina (usually with the 25–26 cm tube mark at the patient's teeth). The operator then proceeded with the TLT as described by Fantoni, but without the use of bronchoscopy. Removal of the narrow ET tube was performed by a nurse at the appropriate time.

Fifty-eight TLTs were performed on 56 patients. No patients needed to be referred for surgical tracheostomy. Mean time from admission to TLT was 4.8 days (range 1–13), and mean duration of cannulation was 8.1 days (range 1–25 days). Sixty-six per cent of patients survived their ICU stay and 46% survived to leave hospital. No patients suffered any bleeding complications despite 13 patients (22%) having abnormal INR (>1.8, highest 5.0 before FFP) and/or thrombocytopaemia ($<50\times10^9$ litre, lowest 7×10^9 litre before platelet infusion). Two patients with severe respiratory failure had mild transient desaturations (Sp_{O_2} 75–90%) during the final stage of insertion.

During one procedure, the wire broke as the tube/dilator was pulled through. The tube was pulled through with forceps and the procedure completed uneventfully.

In two patients, the tube was pulled out of the trachea during rotation. The patients continued to be ventilated with the narrow cuffed ET tube while a second TLT was performed uneventfully.

The ability to perform bedside TLT in the ICU with a single operator facilitates appropriate respiratory management in our unit. The technique described above appears safe. The absence of bronchoscopic visualization is under review but, as the use of bronchoscopy has not prevented posterior tracheal wall damage or inappropriate placement of the tracheostomy in reported series,[2 3] we do not feel that the need for its routine use is proven.

Keywords: equipment, tubes tracheostomy

References

1 Fantoni A, Ripamonti D. *Intensive Care Med* 1997; **23**: 386–92
2 Fernandez L, Norwood S, Roettger R, *et al. Arch Surg* 1996; **131**: 129–32
3 Berrouschot J, Oeken J, Steiniger L, *et al. Laryngoscope* 1997; **107**: 1538–44

Long-term survival after intensive care—subgroup analysis and comparison with the general population

J. C. Wright[1], L. Plenderleith[1] and S. A. Ridley[2]

[1]*Intensive Care Unit, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK.* [2]*Intensive Care Unit, Norfolk and Norwich Acute NHS Trust, Brunswick Road, Norwich NR1 3SR, UK*

We compared the long-term survival of patients admitted to intensive care with that of the general population, and examined the association between age, sex, diagnosis and acute physiology and chronic health evaluation II (APACHE II) score on admission and mortality.

A retrospective observational cohort study was performed with prospectively gathered data on all patients admitted to the intensive care unit from 1985 to 1992, with patients followed up until 1997.

There were 2104 adult patients admitted to the intensive care unit (ICU). These patients were then sub-divided into nine diagnostic subgroups. Vital status at 5 yr was compared with the general population adjusted for age and sex for Scotland. The 5-yr mortality for the ICU patients was 47.1%, 3.9 times higher than that of the general population. For those surviving intensive care the 5-yr mortality was 33.4%. For long-term survivors, the odds ratio of dying (and its 95% confidence interval) compared to the general population did not straddle 1.0 until the start of the fourth year after ICU admission. Thereafter, the odds ratio fell below 1.0 suggesting that in the very long-term survivors (7–9 yr), mortality may be less than that of the general population.

Multivariate analysis showed that risk factors for mortality in those admitted to ICU were age, APACHE II score, and diagnostic category. Mortality was higher for those admitted in the diagnostic categories of haematological disease (87.5%), neurological disease (61.7%), and septic shock (62.9%).

Long-term survival after intensive care is not only related to age and severity of illness but also to the diagnostic category to which the patient belongs. By rounding and scaling the co-efficients, a risk score was produced:

Risk score=10 (age co-efficient+APACHE II coefficient+diagnosis coefficient)

None of the patients with a risk score of greater than 102 survived more than 5 yr and 75% of those who survived to 5 yr had a risk score of 68 or less.

We conclude that the risk of mortality in survivors of ICU matches that of the normal population after 3 yr, and that haematological and neurological diseases together with septic shock carry the highest mortality. Age, severity of illness and diagnosis can be combined to provide an estimate of 5-yr survival.

Keywords: intensive care; critical care; statistics, survival rate

Sedation of ventilated patients in intensive care—a national survey

K. McKinlay, C. P. Rae, L. Anderson and A. R. Binning

General Intensive Care Unit, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK

Sedative agents have the potential to cause morbidity and mortality and prolong recovery.[1] A variety of techniques have been used to provide and monitor sedation in this setting.[2] The aim of this survey was to determine current sedation practice in intensive care in the UK.

A three-page questionnaire containing twelve questions and four case scenarios was sent to the Consultant in Charge of all adult intensive care units in the UK in October 1999. Those units that did not reply were sent another questionnaire. All replies were received by April 2000. Information was requested on the characteristics of the intensive care unit, use of analgesic/sedative drugs, use of a procedure for sedation, use of antidepressants/complementary therapies and their preferred sedation regimen for four given case scenarios. Return envelopes were numbered to identify replies but analysis of the questionnaires was anonymous.

Of the 274 questionnaires sent, replies were received from 195 (71%). Of the units, 193(99%) were general adult Intensive Care Units. The most commonly prescribed sedative was propofol followed by midazolam. The most commonly prescribed analgesic was morphine, then alfentanil. The commonest sedative/opioid combination was morphine/midazolam, followed by propofol/alfentanil. Twenty-seven (14%) units used isoflurane for sedation. A written procedure for sedation was used by 120(62%) units, most commonly the Ramsay scale. One hundred (51%) units attempted to mimic normal sleep patterns, usually by increasing night sedation. More than 10% of patients were prescribed antidepressants in 76 (39%) of units. Thirty-four (17%) units used complementary therapies, mainly aromatherapy or reflexology. A great variety of sedative regimens (80) were provided for the four given case scenarios.

This survey has demonstrated wide variation in prescription of sedative and analgesic drugs in intensive care. It provides a strong argument for rationalization of sedation practice in the UK.

Keywords: intensive care; anaesthetic–analgesic regimens; statistics

References

1 Shapiro BA, Warren J, Egol AB, *et al. Crit Care Med* 1995; **23**: 1596–600
2 Prielipp RC, Coursin DB, Wood KE, *et al. Crit Care Clin* 1995; **11**: 983–1003

Assessing the requirement for high dependency unit beds

H. A. Matthews, **O. A. Williams**, J. A. Grabham, P. P. Musto and D. G. Raitt

Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

A previous study determined that six high dependency unit (HDU) beds were required in a 742-bed acute teaching hospital.[1] Despite these findings, the HDU that was subsequently commissioned contained four beds. In order to ascertain if the HDU requirements of the hospital had changed, the study was repeated during 2000.

Over a 2-week period using identical methods to previously, an investigator visited each of 16 acute wards daily, to identify patients appropriate for HDU admission. Visits were also made to the Department of Critical Care Medicine (DCCM) to identify patients admitted for HDU care, and operating theatre recovery records were examined to identify any patients who required monitoring for more than 3 h after surgery. At each visit to a general ward, the nurse in charge was asked to identify any patients requiring additional nursing care or in need of increased monitoring. Each patient was assessed using the Therapeutic Intervention Scoring System (TISS).[2] A score of greater than 10 indicated suitability for HDU admission. Physiological and biochemical data were then collected to allow calculation of each patient's Simplified Acute Physiology Score (SAPS II)[3] and, hence, calculation of probability of hospital mortality.

The numbers of patients fulfilling HDU criteria, the mean duration of their stay and total patient days were similar. Although TISS scores were similar, the mean predicted mortality of patients in 2000 had almost doubled, implying that patients were sicker, more elderly, and more likely to be receiving emergency treatment. The 'occupancy' by identified patients was similar, supporting the findings of the initial study. Of note was the fact that only 51.6% of patients who fulfilled criteria were admitted to the HDU in the second study. The necessity for closure of HDU beds on some days to provide up to nine ICU beds contributed to this finding. During the study period, seven surgical patients booked into HDU either had their surgery postponed or were managed on the ward instead. This study supports our previous findings, that two more HDU beds are required to fulfil the hospital's requirements. As beds are used flexibly, any expansion of HDU facilities needs to be supplemented by expansion in ICU bed numbers so that encroachment on HDU facilities can be avoided (Table 25).

Table 25 Effects of introduction of HDU

	Pre-HDU (December 1996)	**Post-HDU (January 2000)**
DCCM bed availability in hospital (excluding Renal Unit)	7 ICU	7 ICU plus 4 HDU (or 9 ICU)
Total number of patients requiring additional care	35 (ward)	31 (ward and HDU)
Number of HDU patients admitted to DCCM	–	16 (51.6%)
Total patient days identified	76	79
Mean length of time fulfilling HDU criteria days (range)	2.2 (1–5)	2.5 (1–11)
'Occupancy' by patients identified (no. patients)	5.4	5.6
Mean TISS (range)	14.1 (10–33)	14.8 (10–21)
Mean predicted mortality % (range)	5.71 (0–19.6)	10.60 (0.6–64.0)

Keywords: high dependency

References

1 Williams OA, Grabham JA, Musto PP, Raitt DG. *Br J Anaesth* 2000; **84**: 680P

2 Keene AR, Cullen DJ. *Crit Care Med* 1983; **11**: 1–3

3 Le Gall J-R, Lemeshow S, Saulnier F. *JAMA* 1993; **270**: 2957–63

Comparison of two methods for measuring tidal volumes in patients mechanically ventilated with helium–oxygen mixtures

J. A. S. Ball, A. Rhodes and R. M. Grounds

Intensive Care Unit, St. George's Hospital, Blackshaw Road, London SW17 0QT, UK

In mechanically ventilated patients reducing the density of the inspired gas by substituting helium for nitrogen offers several theoretical benefits. However, accurately monitoring tidal volumes of helium–oxygen mixtures with conventional flowmeters is problematic, as all commonly used devices are adversely affected by changes in gas density. We tested two widely available flowmeters, to ascertain whether reliable and reproducible correction factors could be obtained.

We used an unadapted Galileo ventilator (Hamilton Medical, Switzerland), to which heliox (21% oxygen, 79% helium) was connected via the air inlet. This ventilator measures expired tidal volume utilizing a variable orifice flowmeter (VOF). The circuit was then connected to a Pitot tube flowmeter (MCOVX, Datex-Ohmeda, Finland), which in addition, contains a side stream gas sampler to monitor gas composition. In place of a patient, a mechanical lung (BIO-TEK Instruments Inc., USA) was used, which accurately measures delivered gas volumes independent of gas density. Carbon dioxide was entrained, distal to the flowmeters, just proximal to the mechanical lung, to simulate the clinical setting. Both flowmeters were repeatedly tested across a range of tidal volumes (200–1200 ml).

This method proved to be reliable and reproducible. Inspired (Vti) and expired tidal volume (Vte) as measured by the Pitot tube flowmeter and VOF, when plotted against that measured by the mechanical lung, showed excellent linear correlation (R^2=0.99 for all). From the gradient of these lines, we calculated a set of correction factors (CF). All measurements were repeated five times and averages (Av) and standard deviations (SD) derived (Table 26).

We conclude that both of these devices can be reliably used to monitor respiratory variables in patients mechanically ventilated with helium–oxygen provided gas composition, temperature, and relative humidity are accounted for.

Keywords: monitoring, ventilation; equipment, flowmeters

Patients at risk: validation of early warning score in medical admissions

C. P. Subbe[1], M. Krueger[2] and L. Gemmel[2]

[1]*Department of Medicine and* [2]*Department of Critical Care Wrexham Maelor Hospital, Croesnewydd Road, Wrexham LL13 4TX, UK*

Catastrophic deterioration of ward patients is often proceeded by obvious changes in clinical parameters.[1] The Early Warning Score

Table 26 Correction factors for differing helium–oxygen mixtures with 5% carbon dioxide (mean and SD)

$F_{I_{O_2}}$	**0.21**	**0.30**	**0.40**	**0.50**	**0.60**	**0.70**	**0.80**	**0.90**	**1.00**	**Air**
Pitot tube Vti [helium–oxygen]										
AvCF	1.448	1.286	1.173	1.094	1.020	0.964	0.908	0.882	0.846	0.891
SD	0.031	0.009	0.012	0.005	0.017	0.017	0.013	0.015	0.005	0.005
Pitot tube Vte [helium–oxygen+5% carbon dioxide]										
AvCF	1.499	1.361	1.246	1.166	1.105	1.047	0.984	0.961	0.913	0.962
SD	0.012	0.012	0.012	0.005	0.010	0.012	0.010	0.008	0.015	0.002
VOF (ventilator) Vte [helium–oxygen+5% carbon dioxide]										
AvCF	1.492	1.347	1.228	1.139	1.065	1.006	0.946	0.907	0.883	0.922
SD	0.034	0.017	0.011	0.012	0.014	0.015	0.015	0.015	0.012	0.013

(EWS)^2 is a simple scoring system aimed to identify surgical patients at risk of catastrophic deterioration. It involves respiratory rate (RR), systolic arterial pressure, pulse rate, temperature, and AVPU score. The ability of a modified EWS to identify surgical patients who would potentially benefit from intensive care has been recently demonstrated.[3]

Our aim was to evaluate the ability of a modified EWS to identify medical patients at risk. We also wanted to estimate the workload that use of EWS would generate for nurse practitioners or physicians responding to high EWS.

We performed a prospective observational study in the 56-bed acute medical admissions unit (MAU) of a district general hospital serving a population of 300 000 in North-East Wales. Data from 709 patients were collected twice daily for up to 5 days. Outcomes were death, HDU or ICU admission and survival or discharge at 60 days.

Mean (SD) age of patients was 63 (19) yr. Outcome data were available in 657 patients.

During the observation period 50 of the patients died, six were admitted to ICU and 22 to HDU. EWS-scores ranged between 0 and 9. Fifty-six patients reached high scores of above 4.

High scores were associated with increased risk of death (odds ratio 3.8, 95% confidence interval 1.8–7.9) and ICU admission (odds ratio 5.8, 95% confidence interval 1.04–32.7). There was a trend towards an increased rate of HDU admission.

On the MAU 7% of patients had high scores on admission, 4% on day 2 and 2% on day 3 of their admission. No patient with a normal respiratory rate on admission died or was admitted to HDU. Mortality did increase significantly (P<0.001) with increasing respiratory rate-scores (mortality of 0, 6, 12 and 23% with respiratory rate scores of 0, 1, 2 and 3).

The study confirmed the importance of the respiratory rate to identify critically ill patients. The EWS did identify patients at risk. Its use could lead to earlier identification of critically ill medical patients in need of increased levels of care. It remains to be shown if this would lead to better prognosis of patients and shorter length of stay in critical care units.

The majority of patients appear to have their highest score on admission. Use of EWS in the post-admission period is, therefore, likely to generate only a limited increase in workload for nurse practitioners or physicians responding to high scores.

Keywords: statistics, early warning score

Funding: The study was supported by a grant from the NE-Wales NHS Trust.

References

1 Schein RMH, Hazday N, Pena M, *et al. Chest* 1990; **98**: 1388–92
2 Morgan RJM, Williams F, Wright MM. *Clin Intensive Care* 1997; **8**: 100
3 Stenhous C, Coates S, Tivey M, *et al.* State of the Art Meeting. London: Intensive Care Society, December 1999

Profile of serum protein S-100B release after cardiac arrest: preliminary data

R. G. M. Jackson[1], G. S. Samra[1], G. W. Minto[1], G. H. Clark[2] and C. P. Price[2]

[1]*Academic Department of Anaesthesia and Intensive Care and* [2]*Academic Department of Clinical Biochemistry, Royal London Hospital, Whitechapel, London E1 1BB, UK*

Protein S-100B is a calcium binding protein released from astrocytes after cardiac arrest. Recent published work suggests that serum levels can predict outcome after cardiac arrest.[1 2] However, in these studies single samples were taken in the first 24-h period. Little is known of the profile of release and excretion during this time period. We have, therefore, begun to investigate the profile of serum S-100B release during this time period.

With Ethics Committee approval, we have recruited six patients (five male, one female) admitted to our intensive care unit for ventilation after primary cardiac arrest. Blood was taken from an arterial line at 1, 2, 4, 6, 8, 12, and 24 h after restoration of spontaneous cardiac output. These samples were separated and the serum frozen at –20°C. S-100B was measured using a commercial immunoluminometric assay. Patients had a median age of 68 yr (range 58–78 yr), and a median duration of arrest of 19 min (range 7–30 min). The graph shows the profiles of release of five patients. Patients 1–4 have raised levels that decrease rapidly; sedation was not required beyond 6 h, and all subsequently died within 3 days. Patient 5 shows a less rapid decrease, was mildly hypotensive on inotropes with an adequate urine output, but eventually died on ionotropes and minimal sedation 5 days post-arrest. Patient 6 showed an extremely elevated level of 48 μg litre^{-1} at 1 h, rising to 137 μg litre^{-1} at 4 h, was hypotensive, hypoxic, and oliguric despite increasing levels of ionotropic support, and died 5 h post-arrest.

These patterns of release suggest that time of sample is essential in assessing serum S-100B levels. Early sampling may provide more information on the severity of brain injury. Caution needs to be used in interpreting serum levels after primary cardiac arrest (Fig. 14).

Keywords: protein, serum S-100B; complications, cardiac arrest

References

1 Martens P, Raabe A, Johnsson P. *Stroke* 1998; **29**: 2363–6
2 Rosen H, Rosengren L, Herlitz J, *et al. Stroke* 1998; **29**: 473–7

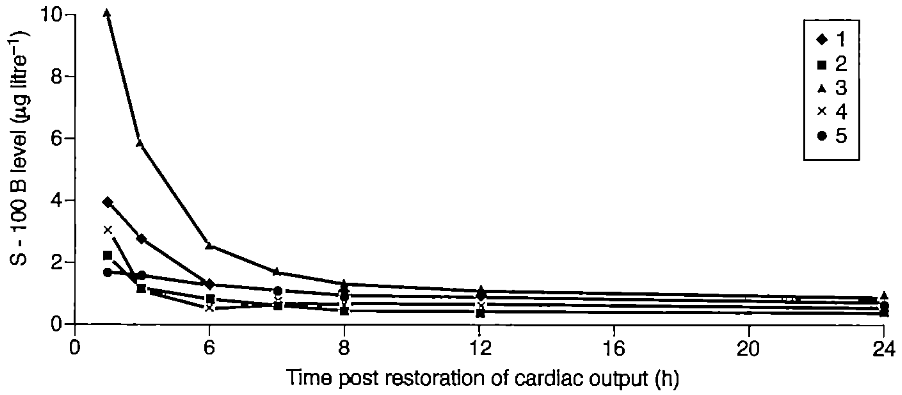

Fig 14 Serum S-100B levels after cardiac arrest.

Table 27 Changes in parameters after 18 h prone positioning

Mean (SEM) n=6	**Pre-prone**	**1 h post-prone**	**2 h**	**6 h**	**12 h**	**18 h**	**1 h after-supine**
Pa_{O_2}/FI_{O_2}	23.1 (2.1)	30.4 (1.2)	30.1 (1.7)	34.9 (2.1)	37.0 (2.6)*	38.1 (2.8)	43.8 (3.0)
V_d/V_t alv	0.78 (0.08)	0.70 (0.05)	0.66 (0.05)	0.66 (0.06)	0.67 (0.06)	0.63 (0.05)	0.62 (0.05)
O_2ER	0.19 (0.02)	0.18 (0.03)	0.21 (0.03)	0.20 (0.02)	0.22 (0.03)	0.24 (0.01)	0.23 (0.02)
EVLWI	16.50 (3.24)	17.00 (3.40)	16.83 (3.57)	15.50 (3.12)	15.00 (2.79)	13.67 (2.33)	12.67 (1.98)
EVLWI/ITBVI	0.02 (0.004)	0.017 (0.003)	0.018 (0.003)	0.017 (0.002)	0.016 (0.002)	0.016 (0.002)	0.0130 (0.003)

Duration of prone positioning in acute respiratory distress syndrome

D. McAuley, S. Giles and F. Gao

Intensive Care Unit, Birmingham Heartlands Teaching Hospital, Bodesley Green East, Birmingham B9 5SS, UK

The optimum duration of prone positioning in acute respiratory distress syndrome (ARDS) is uncertain. Changes in oxygen extraction ration (O_2ER)[1] and extravascular lung water (EVLW)[2] are associated with mortality in ARDS. Alterations in the relation of EVLW to intrathoracic blood volume (EVLW/ITBV) derived from thermal-dye dilution curves indicate changes in pulmonary vascular permeability. Alveolar deadspace to alveolar tidal volume ratio (V_d/V_t alv) examines ventilatory efficiency. This aim of this prospective pilot study, using these parameters, was to determine the optimum duration of prone positioning in ARDS.

Entry criteria included: bilateral pulmonary infiltrates, pulmonary capillary wedge pressure (PCWP) <18 mm Hg, Pa_{O_2}/fraction of inspired oxygen (FI_{O_2}) <27 kPa with an FI_{O_2} of $\geq$0.6 and inverse ratio ventilation with positive end-expiratory pressure (PEEP) >10 cm H_2O on pressure-controlled ventilation for at least 24 h. Patients were turned prone for 18 h. Except for FI_{O_2}, ventilator settings remained unchanged during the study period. V_d/V_t alv was obtained using a CO_2SMO-Plus machine via a volumetric carbon dioxide sensor. EVLW and ITBV were obtained using a single arterial thermodilution technique with a 5F-fibreoptic thermistor femoral artery catheter. Measurements were taken at pre-prone, 1, 2, 6, 12, and 18 h after prone and 1 h after supine. Data are expressed as mean (SEM). Student's t-tests with a Bonferroni correction were used for statistical analysis.

Six (two male) patients (age 19–66 yr) were studied. Although mean Pa_{O_2}/FI_{O_2} improved within 1 h, it continued to improve during the period studied and only reached significance 12 h after proning (37.01 (2.55), P=0.048). All the parameters measured showed trends towards favourable outcome and continued to improve up to at least 12 h after prone positioning (Table 27).

Prone positioning in ARDS may need at least 12 h for maximal benefit.

Keywords: complications, acute respiratory distress syndrome; position, prone

References

1 Hayes MA, Yau EH, Timmins AC, Hinds CJ, Watson D. *Chest* 1993; **103**: 886–95

2 Davey-Quinn A, Gedney JA, Whiteley SM, Bellamy MC. *Anaesth Intensive Care* 1999; **27**: 357–62

Intrathoracic blood volume reflects circulatory volume status in patients with ARDS in the prone position

S. Giles, D. McAuley and F. Gao

Intensive Care Unit, Birmingham Heartlands Teaching Hospital, Bodesley Green East, Birmingham B9 5SS, UK

Central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) have failed to guide fluid management in patients requiring mechanical ventilation because of the influence of positive intrathoracic pressure.[1] These difficulties are magnified in the management of acute respiratory distress syndrome (ARDS) using lung protective ventilatory strategies and prone positioning. Intrathoracic blood volume (ITBV) derived from thermal-dye dilution curves indicates circulating volume rather than pressure. The aim of this prospective pilot study was to investigate the correlation between these indicators of circulating volume (CVP, PCWP, ITBV) and cardiac index (CI) measured using a continuous cardiac output catheter (CI-CCO) and an arterial thermodilution catheter (CI-PiCCO) in ARDS with prone positioning.

Entry criteria included: bilateral pulmonary infiltrates, PCWP <18 mm Hg, Pa_{O_2}/fraction of inspired oxygen (FI_{O_2}) <27 kPa with an FI_{O_2} of $\geq$0.6 and inverse ratio ventilation with positive end-expiratory pressure (PEEP) >10 cm H_2O on pressure-controlled ventilation for at least 24 h. Patients were turned prone for 18 h. Except for FI_{O_2}, ventilator settings remained unchanged during the study period. Values of ITBV and CI-PiCCO were obtained using a single arterial thermodilution technique with a 5F-fibreoptic thermistor femoral artery catheter (Kimal, Pulsion Ltd, UK). Values of CVP, PCWP and CI-CCO were measured using a continuous cardiac output catheter. The relations between the parameters were analysed using Pearson correlation coefficient and linear regression.

Six (two male) patients (age 19–66 yr) with 30 data sets were studied. CI-PiCCO was well correlated with ITBVI (r=0.59, P=0.002) and CI-CCO (r=0.87, P=0.001) (Table 28).

ITBVI more accurately reflected circulatory volume status in ARDS with prone positioning than CVP and PCWP. CI measurements taken from both PiCCO and CCO correlated well. This study suggests that ITBVI should be used rather than CVP or PCWP as an indicator of adequate tissue filling in ARDS fluid management.

Table 28 Correlations between the parameters

	CI-PICCO		CI-CCO	
	r	P	r	P
ITBVI	0.59	0.002	0.04	0.83
CVP	–0.002	0.99	0.26	0.16
PCWP	0.06	0.75	0.75	0.42
CI-PiCCO	–	–	0.87	0.001

Keywords: complications, acute respiratory distress syndrome; blood, volume; position, prone

Reference

1 Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. *Intensive Care Med* 1992; **18**: 142–7

Cardiac troponin I and CK-MB as indicators of myocardial injury after major vascular surgery

R. J. Innes, S. J. Howell and M. S. Suleiman, for the Vascular Anaesthetic Society of Great Britain and Ireland Research Group

Division of Cardiac, Anaesthetic and Radiological Sciences, University of Bristol, UK

The MB fraction of creatine kinase (CK-MB) is one of the biochemical markers of myocardial infarction. It is well known that its use in the perioperative setting is complicated by the fact that it may be released from injured skeletal muscle. In recent years, assays for the cardiac troponins have become available. Cardiac troponin I is specific to cardiac muscle and is not released from injured skeletal muscle. As part of a multi-centre study of perioperative myocardial injury, we collected serial blood samples on post-operative days 1–4 after major vascular surgery in 41 patients. These were analysed using the ACCESS^{TM} analyser and the level of CK-MB and cardiac troponon I (cTnI) determined in each sample. The cut-off for myocardial infarction for troponin I is 0.15 mg litre^{-1} in non-operative patients and we have used this cut-off in the present study.[1] Cut-offs of 4 and 9.4 mg litre^{-1} have been suggested for the diagnosis of myocardial infarction using CK-MB levels determined on the ACCESS^{TM} analyser.[2,3] Taking a diagnosis of myocardial infarction on the basis of a cTnI level >0.15 mg litre^{-1} as the 'gold standard' were determined the sensitivity and specificity of CK-MB using the two cut-off points described above (Table 29).

Table 29 CK-MB and cTnI results

CTnI	CK-MB		CK-MB		Total
	>4.0 mg litre^{-1}	<4.0 mg litre^{-1}	>9.4 mg litre^{-1}	<9.4 mg litre^{-1}	
>0.15 mg litre^{-1}	9	1	9	1	10
<0.15 mg litre^{-1}	13	18	5	26	31
Total	22	19	14	27	41

Using a cut-off of 4 mg litre^{-1} the sensitivity and specificity of CKMB was 0.9 and 0.58, respectively. Increasing the cut-off to 9.4 mg litre^{-1} gave a sensitivity and specificity of 0.9 and 0.83, respectively.

CK-MB is a sensitive indicator of myocardial injury after major surgery. However, significant elevations of CK-MB are also detectable in patients who have not suffered perioperative myocardial injury. The use of the higher cut-off appears to increase specificity without decreasing sensitivity.

Keywords: complications, myocardial infarction; enzymes, creatine kinase

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References

1 Christenson RH, Apple FS, Morgan DL, *et al. Clin Chem* 1998; **44**: 52–60
2 Tun A, Khan IA, Win MT, *et al. Cardiology* 1998; **90**: 280–5
3 Mao GD, Adeli K, Eisenbrey AB, *et al. Am J Clin Pathol* 1996; **106**: 112–7

Catheter related sepsis in critically ill patients on parenteral nutrition

R. Innes and G. Handel

Department of Anaesthetics, Royal United Hospital Combe Park, Bath BA1 3NG, UK

Critically ill patients may have reduced levels of sepsis if commenced on early enteral feed.[1] However, some patients may be intolerant of enteral feed and require total parenteral nutrition (TPN). Several investigators, exploring the effect of TPN on the immune system, have suggested it may be immunosupressive[2] and this could contribute to better outcomes and reduced levels of sepsis seen in enterally fed patients. We, therefore, retrospectively audited the incidence of apparent catheter-related sepsis in parenterally fed intensive care patients.

There were 78 patients with a mean age of 65 (range 18–85). They all had TPN for all or part of their nutritional support whilst on intensive care; mean 8 days (range 5–36, median 5.5). Thirty-two died and 46 survived to hospital discharge.

Thirty-six patients had significant colonization of feeding lines (>15 colony forming units) during their hospital stay and 29 had bacteraemia on blood culture. Twenty patients had probable catheter-related blood infection with the same bacteria present in blood and on catheter tip. Fifty per cent of patients with probable catheter related blood infection died compared with 30% of patients with catheter tip sepsis and 25% with bacteraemia alone.

On average about 5% of central venous catheters lead to blood stream infection.[3] Our audit would suggest infection rates of about 25% with nearly 50% of catheters having significant bacterial colonization, the likely precursor to blood stream infection. These much higher rates reflect the co-morbidity within this population of patients, which make them particularly susceptible to infection. It may, therefore, be appropriate to use antibiotic impregnated catheters in addition to strict aseptic technique during their insertion and maintenance. Finally, these results might suggest that within the general adult, critically ill population TPN actually predisposes to infectious complications as previously suggested in infants[4] and adult oncology patients.[5]

Keywords: complications, infections; equipment, catheters

References

1 Moore FA, Feliciano DV, Andrassy RJ, *et al. Ann Surg* 1992; **216**: 172–83
2 Gogos CA, Kalfarentzoz F. *Nutrition* 1995; **11**: 339–345
3 Maki DG. In: Bennett JV, Brachman PS, eds. *Hospital Infections*, 4th Edn. Philadelphia: Lippincott-Raven, 1998; 689–724
4 Freeman J, Goldman DA, Smith NE, *et al. N Engl J Med* 1990; **323**: 301
5 American College of Physicians. *Ann Inten Med* 1989; **110**: 734

Haemodynamic monitoring in a combined trauma-hypovolaemic shock model

M. Nirmalan[1 3], T. Willard[2], K. Walsh[2], M. O. Columb[2], J. D. Edwards[1 2] and R. A. Little[1]

[1]*MRC Trauma Group, Stopford Building, Manchester M13 9PT, UK.* [2]*Withington Hospital, Manchester M20 2LR, UK.* [3]*Intensive Care Unit, Manchester Royal Infirmary, Manchester M13 9WL, UK*

Cardiac output and pulmonary capillary wedge pressure (PCWP) are frequently used in monitoring circulating blood volume. The adaptation of the double-dye dilution technique (COLD Z-03, Pulsion Medizintechnik) enables a more direct assessment of blood volume and cardiac output using aortic dual dye dilution.[1] [2] As part of a larger study on the consequences of shock we have compared cardiac output values determined by aortic and pulmonary artery thermodilution techniques with changes in blood volume. We have also compared intrathoracic blood volume (ITBV) measured by the COLD system and PCWP to determine which of the two measures correlated better with known changes in estimated circulating blood volume.

Following local animal ethics committee approval, the experiments were carried out in 13 terminally anaesthetized large white piglets (20–30 kg) under Home Office Licence 40/2161. All animals were intubated and ventilated throughout the period of study. A pulmonary artery catheter was passed via the external jugular vein and the arterial dye dilution catheter (Pulsiocath PV 2024; Pulsion Medical Systems) was sited in the abdominal aorta via the femoral artery. After bilateral long bone fractures, known quantities of blood were removed from the arterial cannula at a constant rate ($1\,\text{ml kg min}^{-1}$) to establish pre-defined end points of shock. The animals were maintained in shock for 1 h and then resuscitated with pre-warmed standard resuscitation fluids. At four fixed time points in each experiment 10 ml cold indocyanin green solution (ICG Pulsion $1\,\text{mg ml}^{-1}$) was injected into the right atrium and cardiac output was determined simultaneously using pulmonary artery thermodilution (Baxter VG S2) and aortic thermodilution (COLD Z-03). The COLD system was also used to calculate ITBV. The two measures of cardiac output were compared using Bland-Altman plots and intra-class correlation coefficients (r_i). Within-subject correlation coefficients (r) were used to compare ITBV and PCWP as markers of blood volume.

Our results based on 52 separate measurements show that cardiac output determined by aortic thermodilution were similar to pulmonary artery thermodilution with a bias of −0.28 litre (limits of agreement −0.76, 0.18) and r_i=0.72. Temperature drift in the aorta was not found to be a limiting factor in any of our experiments. ITBV correlated better with estimated circulating blood volume (r=0.92; 95% CI: 0.85–0.96) than PCWP (r=0.62; 95% CI: 0.37–0.78). In some experiments relatively large changes in blood volume (>30% of total blood volume) were associated with no or relatively trivial changes in PCWP. This study shows that the double-dye dilution technique offers considerable advantages in the haemodynamic monitoring of experimental shock models. Further clinical studies are required to determine the implications of these experimental studies in the monitoring of critically ill patients.

Keywords: blood, volume; conplications, trauma; pig

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References

1 Holm C, Melcer B, Horbrand F, *et al. J Trauma* 2000; **48**: 728–34

2 Lichtwarck-Aschoff M, Zeravlk J, Pfeiffer UJ. *Intensive Care Med* 1992; **18**: 142–147

Outcome of children treated in a district general hospital intensive care unit: an assessment of performance using two different scoring systems

N. McGill[1], B. Taylor[1], J. Palmer[1], G. Smith[1], G. Craig[1], M. Tweeddale[1] and J. Pappachan[2]

Departments of Intensive Care Medicine, [1]*Queen Alexandra Hospital, Portsmouth PO6 3LY, UK and* [2]*Southampton University Hospitals Trust, Tremona Road, Southampton SO16 6YD, UK*

Lead centres for paediatric intensive care in England have not been designated on the basis of performance. Our aims were to assess outcome after critical illness when children were treated in a mixed adult and paediatric intensive care unit in a large district general hospital using the Paediatric Risk of Mortality (PRISM) and the Paediatric Index of Mortality (PIM) scoring systems, and to assess the goodness of fit of these two systems.

PRISM and PIM probabilities of hospital mortality were calculated for 345 consecutive paediatric admissions to a 9-bedded mixed adult-paediatric intensive care unit between 1993 and 1998. Predicted and observed mortality were compared using the standardized mortality ratio (SMR) in an attempt to assess unit performance.

Admission rates for the years 1993 to 1998 were 77, 54, 43, 48, 66, and 57. The mean and median ages for the whole group were 6.1 and 4.4 yr, respectively. There were 277 (80.3%) children, 63 (18.2%) infants, and 5 (1.5%) neonates. The mean (median) time from hospital to ICU admission and the mean (median) length of ICU stay were 18 (5) h and 3.4 (1.4) days, respectively. Most admissions (315; 91.3%) were emergency admissions and most patients (221; 64%) were for active intervention, not observation. The sources of admission were: hospital ward 35(39.2%), operating theatre 54 (15.7%), emergency department 54 (30.4%), and another hospital 51 (14.7%).

The unadjusted hospital mortality rate was 4.9% (17). Of the 15 ICU deaths, 14 were expected and resulted from decisions to limit or withdraw treatment; the unexpected death occurred after a cardiac arrest in a 2-yr-old with meningococcal sepsis. The remaining death occurred in a tertiary centre (Table 30).

Table 30 Evaluation of two scoring systems to predict outcome in PICU. **P*<0.05

	Predicted deaths	Observed deaths	SMR [95% CI]
PIM	34.6	17	49 [0.28–0.79]*
PRISM	58.2	17	0.28 [0.16–0.45]*

Both scoring systems discriminated equally well (PRISM ROC 0.85, PIM ROC 0.96; Difference 0.088; P=0.22). The Hosmer-Lemeshow statistics suggested significantly worse calibration for PRISM (C^2=178; P<0.001) than for PIM (C^2=19.8; P<0.05).

These data show that paediatric intensive care can be delivered without excess mortality in mixed general ICUs. This suggests that conclusions drawn from previous studies[1] cannot be generalized and also demonstrates that scoring systems previously used to demonstrate better performance in specialist, as opposed to non-specialist, paediatric intensive care units do not fit the UK data set well.

Keywords: intensive care; children; statistics

Reference

1 Pearson G, Shann F, Barry P, *et al. Lancet* 1997; **349**: 1213–7

Impact of the implementation of a guideline for sedation in the intensive care unit

A. Egan, N. **Sehgal** and D. Sperry

Intensive Care Unit, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

Sedatives are the most commonly prescribed agents in the intensive care unit (ICU), with i.v. sedation forming a high proportion of the pharmaceutical expenditure. There is no ideal sedative agent for use within this patient population. Benzodiazepines and opioids are the most commonly prescribed agents, but dosing these agents can be difficult because of the wide inter-patient variability in the volume of distribution and the clearance of these agents.

During June 1999, ICU records for 35 randomly selected patients admitted during the previous 6 months were studied. Agents used, initial doses, changes in infusion rates, and length of admission were recorded and then analysed to evaluate our sedation practice. Fifteen patients (43%) received midazolam, in 67% of whom the initial dose was between 5 and 8 mg h^{-1}. Propofol was initiated in 29 patients with the majority receiving a starting dose between 10 and 20 ml h^{-1}. Three patients were prescribed propofol for greater than 72 h. Fentanyl was the most commonly used opiate with 27/30 patients (90%) continuing it for 12 h or more. The timing of the changes in the sedative doses was studied and it was demonstrated that most increases in rate were common around midnight whereas reductions occurred during the working day.

The findings of this audit led to the development and implementation of a formal guideline for the prescribing and administration of sedative agents. The guideline was based on the Intensive Care Society Guidelines.[1] It included the use of the Ramsay sedation score and encouraged the use of bolus doses against the background of low infusion rates. Midazolam and morphine were included as the agents of choice for a patient who was to be sedated for greater than 24 h.

After implementation of the guidelines, 35 patients were evaluated using the same criteria as the audit above. 27 patients (77%) received midazolam, in 67% the initial dose was between 0 and 4 mg h^{-1}. Only 33% were started on a dose of 5–8 mg h^{-1}. Twenty patients were given propofol with a similar range of starting doses. Of these 65% were converted to midazolam and nil continued the propofol for greater than 72 h. Only 13 patients received fentanyl during their stay and of these 38% were converted to morphine. In contrast, 23 patients received morphine with 65.2% commenced at a rate of 0–5 mg h^{-1}. Increases in infusion rates were found to be fairly consistent during the 24-h period and fewer increments were made in total. The audit showed an average of 1.74 increases per patient per day compared to a previous value of 11.4.

These data show that the implementation of guidelines in the ICU has had a positive impact in the use of sedative agents. Patients are being sedated with lower doses of drugs, the use of boluses has resulted in infusions being started and maintained at lower levels, and fentanyl and propofol are being used less frequently.

Keywords: anaesthesia, audit

Reference

1 Sedation Guideline Group. *Intensive Care Society National Sedation Guidelines*, October 1999

A comparison of the active heat and moisture exchanging filter with a hot water bath humidifier and a standard heat and moisture exchanging filter

T. B. Pullmood, P. Webb and G. R. Park

John Farman, Intensive Care Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

In the mechanically ventilated, critically ill patient, humidification of the trachea is essential. Under-humidification results in airway plugging, difficulty in oxygenation and damage to ciliary transport. Excessive humidification can lead to profuse secretions.[1] We report the findings of a prospective randomized control trial comparing three different humidifiers. One of these humidifiers, the active heat and moisture exchange filter (aHMEF) comprised a heat and moisture exchange booster (HME Booster® of Tomtec, Belgium) and a standard hygroscopic, heat and moisture exchange filter (HMEF, Medisize Hygrovent S). The HME Booster® is a new concept. It features a heating element covered with a Gore-Tex® membrane. Water is supplied onto the surface of the heater and vaporized to allow passage through the membrane. The membrane regulates the amount of water vaporized.

Consenting patients or patients whose relatives had assented were randomly allocated to have an HMEF alone, an aHMEF or a hot water bath humidifier (HWBH, Fisher & Paykel). The primary end point studied was the number of failures to provide optimal humidification as measured by a secretion score. A score of 1 indicated watery secretions and a score of 4, thick secretions. Normal secretions were given a score of 3.

There were six failures (26%) out of 23 patients in the HMEF group, three (14%) out of 21 in the HME Booster® group and five (23%) out of 22 in the HWBH group. The median secretion score was 2.5 in the HWBH group and 3 in the other two groups. Five failures in the HMEF group required a change in humidification, but only one failure each in the other two groups needed a change.

These data suggest that the aHMEF which comprises of the HME Booster® and HMEF (Medisize Hygrovent S) performs as well as the HWBH (Fisher & Paykel). Its simplicity and lower cost are an advantage.

Keywords: ventilation, mechanical; equipment, humidifiers; lung, trachea

Reference

1 Shelly MP, Lloyd GM, Park GR. *Intensive Care Med* 1988; **14**: 1–9

Ocular microtremor (OMT): a tool for measuring depth of anaesthesia?

S. Bojanic[2], T. Simpson[1] and C. Bolger[1]

[1]*Department of Neurosurgery, Frenchay Hospital, Beckspool Road, Bristol BS16 1LE, UK.* [2]*Department of Neurosurgery, The Radcliffe Infirmary, Woodstock Road, Oxford OX2 1HE, UK*

Ocular microtremor (OMT) is a fine high frequency tremor of the eyes caused by extraocular muscle activity stimulated by impulses emanating in the brainstem.[1] Several studies have shown that the frequency of this tremor is reduced in patients whose consciousness is reduced by anaesthesia or head injury.[2] [3] OMT could, therefore, possibly be used to determine depth of anaesthesia.

Twenty-two unpremedicated subjects undergoing surgery with general anaesthesia were studied. OMT activity was measured at admission using the open eye piezoelectric strain gauge technique.

Anaesthesia was induced with propofol using a target controlled infusion delivery system (Diprifusor). OMT activity was then recorded at predicted plasma propofol levels of 1, 2, 3, and $5\,\mu g\,ml^{-1}$. The patient's level of consciousness (response to command or stimulation) was assessed after each OMT measurement. OMT activity was reduced progressively at predicted plasma levels of propofol of 1 and $2\,\mu g\,ml^{-1}$ and then plateaued between 3 and $5\,\mu g\,ml^{-1}$. There was a significant difference between the last awake OMT recording and the first recording at loss of consciousness ($P<0.001$).

Thus, OMT recording holds promise as a practical indicator of the depth of anaesthesia.

Keywords: anaesthesia, depth; measurement techniques, ocular microtremor

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References

1 Coakley D. *Minute Eye Movement and Brain Stem Function*. Boca Raton: CRC Press, 1983; 59–6
2 Coakley D, Thomas J, Lunn J. *Br J Anaesth* 1981; *Proceedings of the Anaesthetic Research Society*; 1122–23
3 Shakhnovich A, Thomas J, Dubova S, Milovamova L. *Resuscitation* 1980; **8**; 243–55

Critical illness polyneuropathy (CIP)

S. Shah, S. Grundler, N. Stallard and M. N. Smithies

Critical Care Directorate, University Hospital of Wales, Cardiff CF4 4XW, UK

We tested the hypothesis that CIP is related to severity of illness, multiple-organ dysfunction and duration of intensive care stay.

We reviewed all patients with newly diagnosed polyneuropathy on the ICU between March 1999 and March 2000. All patients had new onset, generalized weakness, bilateral absent reflexes, and underwent nerve conduction studies (NCS) during their ICU stay.

We identified eight patients with CIP. Five of the eight patients had abnormal NCS with axonal sensory motor polyneuropathy. In two patients, NCS were difficult to interpret for technical reasons and one patient had normal NCS despite the clinical presentation. The median length of ICU stay before diagnosis was 16.5 days (range 10–35 days), median length of ventilated days after diagnosis was 22.5 (range 12–54), and median total stay on ICU was 34 days (range 20–54) (Table 31).

Table 31 DOA=date of admission; DOT=date of test; W=worse. All values as median (ranges)

APACHE II score			SAPS II score		
DOA	DOT	W	DOA	DOT	W
23.5(10–32)	21(11–32)	33(26–39)	50.5(36–59)	57(35–70)	37(16–70)

We conclude that CIP occurs with prolonged ICU stay and is related to the severity of multiple-organ dysfunction syndrome. The diagnosis of CIP is associated with subsequent prolonged ventilation and has substantial resource implications.

Keywords: complications, polyneuropathy

Reference

1 Bolton CF, Breuer AC. *Muscle Nerve* 1999; **22**: 419–23

Meningococcal disease. Are there differences between the management in adults and paediatric patients?

S. Shah, R. Self, G. Findlay and M. N. Smithies

Critical Care Directorate, University Hospital of Wales, Cardiff CF4 4XW, UK

Neisseria meningitidis is the single biggest cause of death amongst children from infectious causes in the UK. In 1998 there were about 2500 proven cases of meningococcal disease, which resulted in 246 deaths in UK.

The purpose of the study was to identify the differences in the level of awareness and the therapeutic interventions in the paediatric *vs* the adult population in the area served by the University Hospital of Wales.

We studied patients admitted with meningococcal disease admitted to intensive care at the University Hospital of Wales, from 1 January 1997 to 31 December 1998 (Table 32).

Table 32 ICU admission for meningococcal disease (median [range]). Four of the five deaths occurred within 24 h of admission

	Adult	Children
Number	15	20
Average age (yr [range])	23 [15–69]	01 [0–12]
Average meningitis score	9 [3–12]	11 [5–15]
Lumbar puncture (%)	45	10
Inotropes (%)	45	90
Prostacyclin (%)	40	85
Renal replacement therapy (%)	30	32
Rifampacin (%)	40	95
Colloids given in first 12 h on ICU ($ml\,kg^{-1}$)	82	170
Time from hospital admission to ICU (h)	5.4	2.6
Mortality (%)	20	10

We conclude that the paediatric patients were referred earlier to the ICU, were sicker on admission and received more aggressive fluid resuscitation and other therapeutic intervention. They had better outcomes. This possibly reflects the fact that there is a greater awareness of meningococcal disease amongst paediatricians.

Keywords: infection, bacteria; adults; children

Reference

1 Pollard AJ, Britto J, Nadel S, *et al. Arch Dis Child* 1999; **80**: 290–6

Percutaneous tracheostomy: Ciaglia Blue Rhino vs the basic Ciaglia technique of percutaneous dilatation tracheostomy

S. Shah and P. Morgan

Intensive Care Unit, University Hospital of Wales, Cardiff CF14 4XW, UK

Ciaglia described his technique of percutaneous dilatational tracheostomy (PDT) in 1985. It has become the most popular technique for percutaneous tracheostomy and is as safe as the surgical technique. In 1999, a modified technique of PDT was introduced, the Caglia Blue Rhino (CBR), that consists of a one-step dilatation by means of a curved dilator.

To demonstrate the safety and practicability of the Ciaglia Blue Rhino in our intensive care unit we undertook a prospective trial of 60 consecutive patients needing a tracheostomy, on the intensive care unit, using the Blue Rhino technique. We collected the patient characteristics, indication, number of ventilated days before tracheostomy, oxygenation and ventilatory data perioperatively and post-operatively, and complication rate (Table 33).

Table 33 Patient demographics and complications. Results are range (median)

Age (yr)	15–88 (58)
Sex (F:M)	2:3
Duration of ventilation before CBR (days)	0–19 (4)
Ventilatory parameters before CBR	
F_{IO_2}	0.23–0.75 (0.4)
PEEP (cm H_2O)	0–15 (5)
Complication	3 (5%)
Bleeding	3
Sub-cut emphysema	0
Infection	0

We performed a percutaneous tracheostomy in 60 consecutive patients needing a tracheostomy, using the CBR technique. The patient characteristics are as shown in Table 22. The duration of ventilation before tracheostomy was 4 days (0–19 days) with the predominant indication being weaning. The patients were sedated and paralysed before the procedure and ventilated on BiPAP mode. There were three (5%) complications noted, for example, bleeding as compared with 5–15% noted for the serial PDT technique. All three needed blood transfusions to improve haemodynamic status and one needed surgical intervention. There were no subcutaneous emphysema or pneumothorax, nor were any infection of the stoma site noted.

We conclude that CBR technique is equally safe and simpler as compared with conventional serial PDT technique.

Keywords: equipment, tubes tracheostomy

Pilot study of a nurse led critical care outreach service

D. Bright, T. Newman, I. Dyer, D. Rosser and S. Sinclair

University Hospital Birmingham NHS Trust, Selly Oak Critical Care (SOCC) Unit, Selly Oak, Birmingham B29 6JD, UK

Recently 'Comprehensive Critical Care 2000' (Department Health) and 'Critical to Success 2000' (Audit Commission) proposed the necessity for the development of critical care outreach teams. We realized that many of the patients who develop critical illness were initially coming to the attention of the acute pain team. Central to the effectiveness of an outreach team must be familiarity and ease with ward based working practice and ward staff. We set out to pilot a combined outreach and acute pain team and wish to report the activity of this team.

We conducted a 6-month pilot study from January to June 2000 at Selly Oak Hospital, UHB Trust. The team consisted of two G grade nurses—a pain nurse with a critical care background, another seconded from the ICU. The team operated weekdays 09:00–17:00 supported by SOCC staff. The pilot was widely publicized and its objective of clinical and educative support of ward staff at the bedside clearly explained. The team reviewed, with the ward staff, intermediate/major post-operative surgical and trauma patients, and acute medical and surgical admission causing concern to the ward nurses, physiotherapists and trainee medical staff. Critical care discharges were followed up, all patients with a tracheostomy, epidural and central lines *in situ* and any patients causing concern to medical, nursing or physiotherapy staff. 'Causes for concern' were specifically *not* proscribed, a culture of call for help and support was actively encouraged and made possible because the team routinely visited the wards and spent time with the staff there.

A total of 402 patients were reviewed. Of these, 182 were discharges from SOCC (83% of all SOCC discharges during this time period) including 39 patients with tracheostomy. The referral (*refs*) pattern is described below. *Interventions* that were felt, subjectively, to materially to improve an individuals' condition (pain management. venous access and fluid management advice, minitracheostomy, etc.) and *minor problems* (advice, simple teaching, etc.) are summarized. In addition, patients were identified for whom ICU admission would be *inappropriate* after appropriate discussion with managing teams (Table 34).

Table 34 Use of critical care outreach service

	Nurse refs (95)	**Doctor refs (73)**	**Other refs (52)**	**Totals (% of 220)**
Admit SOCC	15	20	7	42 (19)
Interventions	20	27	12	59 (27)
Minor problems	40	14	17	71 (32)
Inappropriate	20	12	16	48 (22)

Critical care outreach as a nurse-led service is feasible and practicable. Uptake outside of routine follow-up has been considerable. It has been well received by the wards.

Enhanced communication between the wards and critical care unit has enabled smoother admissions and discharges. One of the teams' core objectives was to assist the wards in identifying those patients potentially at risk of critical illness, and help co-ordinate their responses by providing practical support and guidance and facilitate multidisiplinary collaboration. This appears to have been successful. It would appear that some 'futile' admissions to ICU could be averted by timely discussion between critical care and ward teams facilitated by the outreach service.

Keywords: intensive care, audit

Introduction of a critical care outreach team improves ward-based nurses confidence in dealing with specific support therapies

D. Bright, T. Newman, S. Brudney, D. Rosser, I. Dyer and S. Sinclair

University Hospital Birmingham NHS Trust, Selly Oak Critical Care (SOCC) Unit, Selly Oak, Birmingham B29 6JD, UK

We planned to pilot a critical care 'Outreach' team to the acute wards at this hospital. In December 1999, we conducted a questionnaire survey of nurse attitudes, on the surgical and trauma wards, at Selly Oak Hospital, UHBTrust, where it was anticipated that the team would be most active. This was repeated in July 2000 after completion of the 6-month pilot study.

The outreach team consisted of two G grade nurses with a critical care background and were supported from SOCC staff. The team operated weekdays 09:00–17:00. The pilot was widely publicized after the first survey and its objective of clinical and educative support of ward staff at the bedside clearly explained. A culture of 'call for help' was actively encouraged. This was possible because the team proactively visited the wards, reviewing SOCC follow-ups, major post-operative and acute pain patients, and spent time with the ward staff.

The questionnaire asked the ward nurses to rank, on a scale of 0–5, how confident they felt when dealing with the following: 1, tracheostomies (T); 2, acutely deteriorating patients (Acute); 3, central venous lines (CVP). In addition they were asked to rank how well-supported they felt by: 1, other nurses (N); 2, medical staff (M); 3, the overall general environment in which they worked (Gen). '0' represented 'disagree strongly' with the statement 'I am confident caring for … /am well supported by … ', '5' represented 'agree strongly'. Finally, they were asked to make any written comments they wished. The questionnaire was conducted in confidence assuring anonymity of respondents. Response rate was 62% pre-outreach pilot and 70% post-outreach pilot (Table 35).

Table 35 Per cent respondents who ranked their confidence or support as 0–2, these being the nurses who feel least confident and supported

	T	Acute	CVP	N	M	Gen
Pre-outreach (*n*=67) (%)	36	14	28	13	42	12
Post-outreach (*n*=76) (%)	17	14	14	5	27	4
P-value	<0.01	NS	<0.1	0.15	0.1	0.14

The comments pre-outreach demonstrated more vociferous complaints about how isolated some nurses feel with some sick patients than even these figures demonstrate. The general post-outreach comments made were without exception supportive, appreciative of the outreach service.

In summary, the introduction of a critical care outreach team seems to improve the confidence of some ward nurses. Whilst confidence does not necessarily correlate with competence it is difficult not imagine the probable benefits of encouraging a more confident, well supported nurse. It apparently halved the number of nurses who are seriously uncomfortable with caring for tracheostomy patients. This questionnaire method will contribute to development of the future direction of the outreach team.

Keywords: intensive care, audit

Comparison of the use of human albumin solution (HAS) in the critically ill, 1998–1999

P. L. Saravanan, S. G. Simms, J. A. Gedney and P. G. Lawler

Intensive Care Unit, South Cleveland Hospital, Middlesbrough TS4 3BW, UK

A meta-analysis of the use of human albumin solution (HAS) as a resuscitation fluid-revealed increased mortality in albumin treated patients.[1] This led to a wide spread change in albumin use.

The aim of the study was to audit the use of human albumin in a group of patients admitted to the intensive care unit at South Cleveland Hospital, Middlesbrough, in a period preceding the publication of this meta-analysis and compare it with the same period following the recommendations.

Fifty consecutive patients between the months of March to July 1998 and the same number of consecutive patients between March and August 1999 were included in the study. All patients whose length of stay in ICU was less than 24 h were excluded. These patients were analysed for age, sex, admission APACHE score, albumin usage, use of other colloid solutions, length of stay in ICU, and outcome expressed as mortality and mortality ratio (MR) (Table 36).

Table 36 Use of albumin and colloid in ICU 1998 *versus* 1999

Year	Sex (m:f)	Age (yr)	Median APACHE	HAS 4.5% (L)	HAS 20% (L)	Colloid usage (L)	ICU (days)	Mortality (%)	MR
1998	24:26	56.9	19	7.1	4.4	55.2	10.3	32.0	0.9
1999	30:20	63.4	20	2.8	2.7	111.8	8.9	42.0	1.2
P value		0.043		0.009	0.184	0.002	0.492		

This audit has confirmed that albumin usage has decreased after the publication of the meta-analysis. However, non-albumin colloid usage (starches) has increased significantly. We failed to demonstrate an improvement in outcome after the decreased use of albumin. This may be because of a difference between the patient groups not identified by median APACHE or may be because of a detrimental effect of the use of colloid either because of the choice of colloid or the volume used. Other studies have also failed to reproduce the deleterious effect of albumin on outcome,[2] have postulated a beneficial role for albumin in septic patients[3] or have demonstrated a worse outcome in patients resuscitated with colloid rather than crystalloid.[4] Our response to the meta-analysis of reducing albumin usage but significantly increasing colloid (starch) usage has not been shown to improve outcome and might have been detrimental.

Keywords: protein, albumin

References

1 Cochrane Injuries Group Albumin Reviewers. *BMJ* 1998; **317**: 235–40

2 Ferguson ND, Stewart TE, Etchells EE. *Intensive Care Med* 1999; **25**: 323–5

3 Quinlan GJ, Margarson MP, Mumby S, Evans TW, Gutteridge JM. *Clin Sci* 1998; **95**: 459–65

4 Schierhout G, Roberts I. *BMJ* 1998; **316**: 961–4

The effect of H^+ concentration on electron transport chain function in hepatocytes

S. Nath, D. Rosser and M. Manji

Department of Intensive Care, University of Birmingham, Edgbaston, Birmingham B15 2TH, UK

In the clinical setting, sepsis and multiple organ failure are characterized by metabolic acidosis, despite adequate oxygen delivery to tissues/cells, suggesting impairment in the ability of tissues to extract oxygen. Evidence has emerged over recent years that this dysfunction in cellular metabolism occurs, in part, as a result of a defect in the mitochondrial electron transport chain. Exposing cells to endotoxin causes a loss of reserve in the respiratory function of the cells.[1] There are many postulated controls of cellular respiration, including hypoxia[2] and $[H^+]$.[3]

Using the methodology described previously by our group[1 2] we assessed the effect of different $[H^+]$ on oxygen consumption rate (OCR) within the experimental field as a marker of mitochondrial electron transport chain function in an *in vitro* model. HepG2 cells were incubated under standard conditions and were then prepared for the experiments in which the cells were resuspended in assay medium of varying pH status. Oxygen consumption studies were performed using a porphyrin

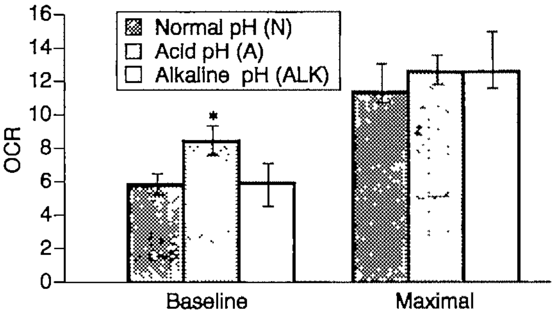

Fig 15 Results: mean (SD) OCR (Torr s $cell^{-1} \times 10^{-8}$) pre- and post-FCCP. ANOVA with post-hoc analysis. *$P<0.05$. Ratios (post-/pre-): N=1.95; A=1.49; ALK=2.14.

phosphorescence quenching technique by serially measuring oxygen tension before and after the introduction of a mitochondrial uncoupler (FCCP). The cellular OCR was calculated using Microsoft Excel to give baseline (pre-FCCP) and maximal (post-FCCP) values for each experiment (Fig. 15).

Acidic conditions significantly increase baseline OCR. This effect may be explained by one of several mechanisms: (1) the pH gradient across the inner mitochondrial membrane increased by the addition of $[H^+]$ stimulates the electron transport chain independent of ATP synthesis. (2) The chemiosmotic theory predicts alteration in mitochondrial respiration by change in pH gradient or increase in the redox potential across the electron transport chain. (3) The increased $[H^+]$ outside the mitochondrial matrix may encourage these protons to return down their gradient via a proton leak. The underlying significance of this observation is uncertain. Our results suggest (ratio post-/pre-FCCP) that an increase in baseline OCR in an acidic environment, renders these cells incapable of increasing ATP production at times of increased demand.

Keywords: oxygen, consumption

Funding: This project has been funded by the United Birmingham Hospitals Endowment Fund.

References

1 Drosser R, Manji M, Cooksley H, Bellingan G. *ICM* 1998; **24**: 725–29
2 Nath S, Bellingan G, Clutton-Brock T, Manji M, Rosser D. *Br J Anaesth* 1999; **82**: 788P–89P
3 Brown G. *Biochem J* 1992; **28**: 1–13

Changes in oxygenation after percutaneous tracheostomy

M. R. Carpenter, J. A. Gedney, F. L. Clarke and P. G. Lawler

Intensive Care Unit, South Cleveland Hospital, Marton Road, Middlesbrough TS4 3BW, UK

Tracheostomy is a common intensive care procedure with rare but important complications.[1] There is a widely held belief that oxygenation deteriorates during and immediately after the procedure. No study to date has looked at oxygenation before and after percutaneous tracheostomy. The aim of this study was to determine the changes in oxygenation after percutaneous tracheostomy and to define any factors predictive of decreased oxygenation.

We retrospectively reviewed the notes of the last 50 consecutive patients undergoing Ciaglia dilatational percutaneous tracheostomy in our unit over a 15-month period. All patients were ventilated on 100% oxygen for the procedure, and over the following hour the fraction of inspired oxygen (FI_{O_2}) was reduced towards pre-procedure levels guided by pulse oximetry. Arterial oxygen tension (Pa_{O_2}), FI_{O_2}, Pa_{O_2}/FI_{O_2} ratio, mode of ventilation and positive end expiratory pressure (PEEP) were recorded before the procedure and at 1 and 12 h post-tracheostomy. Before analysis of the data significant risk to patient well-being was defined as a post-procedure FI_{O_2}0.9 or a post-procedure Pa_{O_2} <8 kPa.

Two patients were excluded, as full data were not available. The mean (SD) age was 69 (13). There were 28 males. Changes in oxygenation are illustrated in Table 37. (All data mean (SD).)

Overall, there was no significant change in oxygenation post-tracheostomy. However, in 29 patients the post-procedure Pa_{O_2}/FI_{O_2} ratio decreased after tracheostomy and one patient was at significant risk. Further analysis of our data failed to show any correlation between an initial high FI_{O_2}, high PEEP, low Pa_{O_2}/FI_{O_2} ratio, or the use of pressure controlled ventilation and a decrease in Pa_{O_2}/FI_{O_2} ratio post-tracheostomy.

Table 37 Changes in oxygenation, all data mean (SD)

	Pre-procedure	1 h post	12 h post
FI_{O_2}	0.45 (0.11)	0.59 (0.12)	0.47 (0.12)
Pa_{O_2} (kPa)	11.6 (2.2)	15.4 (9.7)	13.0 (2.4)
Pa_{O_2}/FI_{O_2} ratio (kPa)	27.5 (9.6)	26.8 (12.1)	29.9 (9.3)

No significant change in oxygenation was seen in this study. Reduction in PEEP or minute volume, soiling of the trachea or the cardiovascular effects of increased sedation could all be expected to reduce the Pa_{O_2}/FI_{O_2} ratio after tracheostomy. A significant deterioration in Pa_{O_2}/FI_{O_2} ratio could have occurred immediately after tracheostomy and improved by 1 h. This would have been masked by the high FI_{O_2}over this period. More frequent blood gas analysis would be required to detect this deterioration.

Tracheostomy offers considerable advantages to intensive care patients. Despite the overall absence of a decrease in the oxygenation post-procedure deterioration did occur in some patients. It was not possible to predict which patients would deteriorate.

Keywords: equipment, tubes tracheostomy; complications, oxygenation deterioration

Reference

1 Dulguever P, Gysin C, Perneger TV, *et al. Crit Care Med* 1999; **27**: 1617–25

The use of an adapted anaesthetic simulator for the training of intensive care nurses

M. P. Oram, J. Ingham, M. Swart, J. Carlisle and D. Sinclair

Intensive Care Unit, Torbay Hospital, Torquay TQ2 7AA, UK

The use of computer-based simulators has been described in the training of anaesthetists,[1] [2] intensivists[2] and anaesthetic assistants,[3] but not ICU nurses. Simulators allow the participant to gain experience of situations that may occur infrequently in their clinical practice without risk to real patients.

The 'Access' anaesthetic simulator[1] consists of a manikin attached to a computer and monitor. The computer displays an electrocardiogram, oxygen saturation, intermittent non-invasive arterial pressure monitor, and end-tidal carbon dioxide value. Thirty ICU nurses took part in three simulated scenarios each. The scenarios consisted of (1) asystole, (2) anaphylaxis, and (3) hypotension after a bolus of propofol. The nurses undertook the immediate management of the scenario as they would in 'real-life' before the arrival of medical staff. For the purpose of the study, the manikin was intubated, ventilated with an ICU ventilator, and attached to infusion pumps. Following the scenario, time was allowed for feedback from the investigators. Various components of the simulator were then scored between 1 and 10 (poor and excellent respectively) on an anonymous questionnaire, space was also allowed to suggest improvements and detail the length of their intensive care experience.

Thirty nurses took part in the study, their ICU experience ranged from 3 months to 20 yr. The average scores given to each component were: the monitor 5.5, the manikin 8.0, the scenarios 8.1, the infusion pumps 8.5, the ventilator 8.7, the overall experience 9.2, and the usefulness for training 9.4. The improvements they suggested concerned the display of the monitoring. This was different to the ICU monitor used by the nurses studied, in particular the lack of continuous invasive pressure waveforms.

Overall, the nurses found the simulator a very useful tool and were keen to develop its use for training. The suggestions made concerned the monitoring. If monitors commercially available for ICU were incorporated into the simulator, it would improve the use of the simulator for training nurses in ICU.

Keywords: education; equipment, computer-based simulator

Funding: Supported by a grant from the Torbay Hospital Special Medical Projects Trust.

References

1 Byrne AJ, Jones JG. *Br J Anaesth* 1997; **78**: 553–6
2 Arne R, Stale F, Ragna K, *et al. Int J Clin Monit Compting* 1996; **13**: 147–52
3 Ashurst N, Rout CC, Rocke DA, *et al. Br J Anaesth* 1996; **77**: 468–72

Tonometry-guided therapy: an algorithm-testing pilot study

R. Hurley, M. P. W. Grocott, **M. Silva**, C. Goldsack, J. Frossard and M. G. Mythen

Centre for Anaesthesia, UCL, London W1N 8AA, UK

Abnormal gastric perfusion measured using gastric tonometry is associated with poor outcome after major surgery.[1] Clinical trials using tonometry-guided therapy do not show an outcome improvement.[2] Studies to date have not demonstrated a treatment algorithm resulting in correction of abnormal tonometry-derived measurements.

An uncontrolled algorithm-testing pilot study was conducted. Twelve patients having elective high-risk non-cardiac open major surgery were recruited. Gastric intra-mucosal to end-tidal carbon dioxide gap ($P_{CO_2} - E'_{CO_2}$) was monitored using gastric tonometry and the TONOCAP® monitor. An increase in the gap of $\geq$0.5 kPa above baseline triggered a resuscitation algorithm involving central venous pressure-guided volume expansion in stage 1. Failure to correct the gap at stage 1 initiated stage 2-cardiac output (CO) measurement and institution of either dobutamine (low CO) or dopexamine (normal CO) therapy. The primary outcome variable was an end of surgery gap of $\leq$0.5 above baseline.

Six patients developed an abnormal $Pg_{CO_2} - E'_{CO_2}$ gap and were commenced on the treatment algorithm. In stage 3 the gap was corrected by the end of surgery (Table 38).

Table 38 Patient details and tonometry variables

Case	ASA	Operation	Baseline gap	Max^{m} gap	Gap	Treatment	End of surgery gap
1	2	Radical prostatectomy	1.8	2.0	No		No
2	2	Partial nephrectomy	0.4	2.5	Yes	Fluid	Yes
3	3	Right hemicolectomy	0.4	0.9	No		No
4	3	Laparotomy	1.3	1.9	Yes	Fluid	No
5	2	Partial hepatectomy	1.7	2.2	Yes	Fluid and dopexamine	No
6	2	Right hemicolectomy	2.6	2.6	No		No
7	3	Left nephrectomy	0.7	1.4	Yes	Fluid	No
8	2	Radical prostatectomy	1.9	2.3	No		No
9	3	Laparotomy	5.1	5.1	No		
10	3	Radical cystectomy	1.2	2.2	Yes	Fluid and dobutamine	Yes
11	3	Right hemicolectomy	1.5	1.5	No		No
12	2	Laparotomy	0.0	1.1	Yes	Fluid	Yes

We have demonstrated an algorithm capable of resolving an abnormal $Pg_{CO_2} - E'g_{CO_2}$ gap.

Keywords: measurement techniques, gastric tonometry

References

1 Bennett-Guerrero E, Welsby I, Dunn TJ, *et al. Anaesth Analg* 1999; **89**: 514–9
2 Pargger H, Hampl KF, Christen P, *et al. Intensive Care Med* 1998; **24**: 769–77

The modified early warning system: implementation in a district general hospital

S. Coates, M. Tivey, P. Allsop and C. Stenhouse

Intensive Care Department, Queen's Hospital, Burton Hospital NHS Trust, Belvedere Road, Burton on Trent, Staffordshire DE13 0RB, UK

We have developed the modified early warning system (MEWS)[2] from the previously described early warning score (EWS).[1] Since its introduction in 1998, 634 surgical patients have fulfilled the ward-based criteria for observation on the system. This represents 12.7% of all admissions to the two wards used for this study. A total of 16 533 sets of observations were made on these patients. We restricted the study to two wards so that the process of implementation could be analysed. Initially one ward was allowed to enrol any patient whilst the other ward was given strict guidelines. It rapidly became apparent that guidelines were required on both wards. Other key points from this study were as follows. The use of a combined observation and MEWS chart[3] prevented data duplication. Set a realistic 'trigger' score, in our study a score of four or more resulted in medical referral, not necessarily intensive care admission or involvement. The referral guidelines were agreed before commencement with the surgical teams. Regular feedback to the wards is vital, as is a clerk to facilitate data collection from the MEWS.

Sub-optimal care on the ward before intensive care admission has been identified as a contributor to later mortality and morbidity.[4] Education and communication were highlighted as two areas of inadequacy. The MEWS has provided an opportunity to introduce continuing multidisciplinary education at ward level and to improve communication between the wards and the intensive care. Improved awareness of patient dependency has also resulted in an improvement in skill mix at the ward level.

During the first 9 months, we identified 11 patients who were admitted to the ICU from the study wards but who were not on the MEWS. At this point further education took place and inclusion criteria were modified. In the last 15 months, no patients have been missed. Initially the MEWS resulted in an increased workload for the on call ICU doctors but the educative approach to the ward management of these patients has resulted in a reduced but appropriate referral pattern.

Finally, this tool has aided multidisciplinary physiological assessment and provided a resource for education and change. Critical care is no longer within the confines of the intensive care unit.

Keywords: critical care; complications, modified early warning system

References

1 Morgan RJM, Williams F, Wright MM. *Clin Intensive Care* 1997; **8**: 100
2 Stenhouse C, Coates S, Tivey M, Allsop P, Parker T. *Br J Anaesth* 2000; **84**: 663
3 McQuillan P, Pilkington S, Allan A, *et al. BMJ* 1998; **316**: 1853–8

An analysis of physiological variables in ward surgical patients being monitored using the Modified Early Warning System (MEWS) to detect developing critical illness

C. W. Stenhouse, S. Coates, M. Tivey and P. Allsop

Intensive Care Department, Queen's Hospital, Burton Hospitals NHS Trust, Belvedere Road, Burton on Trent, Staffordshire DE13 0RB, UK

Derangement of physiological variables have been demonstrated up to 8 h before cardiac or respiratory arrest.[1] [2] Increased risk of death has also been shown in patients with pneumonia who have high respiratory rates, low systolic arterial pressure or confusion.[3] It has been suggested that changes in the clinical process to improve recognition of physiological abnormalities and to make ward staff more aware of the significance may improve quality of care before admission to intensive care.[4]

The Modified Early Warning System (MEWS)[5] was developed as a simple scoring system using routine ward based observations to score a patient's physiological derangement. MEWS was introduced on two general surgical wards and during a 2-yr-period 634 patients at risk of developing critical illness have been observed using this system. An analysis of the physiological variables namely respiratory rate, heart rate, systolic arterial pressure, temperature, urine output, and mental status is shown (Fig. 16).

Increased respiratory rate is a sensitive and early indicator of a patient developing critical illness on a general surgical ward.

Keywords: critical care; complications, modified early warning system

References

1 Franklin C, Mathew J. *Crit Care Med* 1994; **22**: 244–7
2 Schein RM, Hazday N, Pena M, *et al. Chest* 1990; **98**: 1388–92
3 Neill AM, Martin AR, Weir R, *et al. Thorax* 1996; **51**: 1010–1016
4 McQuillan P, Pilkington S, Allan A, *et al. BMJ* 1998; **316**: 1853–8
5 Stenhouse C, Coates S, Tivey M, Allsop P, Parker T. *Br J Anaesth* 2000; **84**: 663P

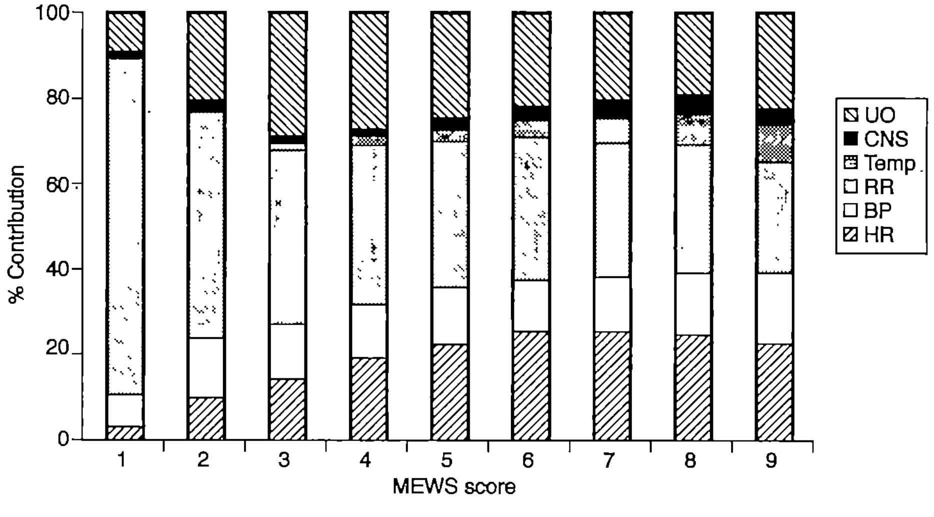

Fig 16 An analysis of the physiological variables namely heart rate (HR), systolic arterial pressure (BP), respiratory rate (RR), temperature (Temp), mental status (CNS), and urine output and MEWS score.

Bereavement follow-up in intensive care

K. A. Dillon, S. J. Coates and C. W. Stenhouse

Department of Intensive Care, Queens Hospital, Burton Hospitals NHS Trust, Belvedere Road, Burton on Trent, Staffordshire DE13 0RB, UK

Caring for the dying and their families is an important part of the Intensive Care Unit (ICU).[1] The relatives of ICU patients generally receive a huge amount of emotional support whilst within the intensive care setting; however, once the patient dies this ceases. The bereavement follow up service commenced within Queens ICU following guidelines from the Intensive Care Society in 1998.[2] The service found 22% of all relatives returned to the unit in the first year's data collection (1999).

Initial contact was made before the relative's departure from the unit after the death. The database within the unit highlighted all relatives to be contacted at 6–8 weeks. Only relatives who replied were contacted further and offered a 1-h appointment in a private room within the unit. All notes were retrieved and read by the nurse before the visit and an ICU consultant was made aware of their return.

The positive findings were that communication and the opportunity to return to the service was seen as very good, and the care they and their relative received was excellent. From a negative aspect, of all the relatives seen 74% of patients had treatment withdrawn before death. These relatives returned with feelings of guilt surrounding this. Tracheal tubes (ET) being present on death caused distress. Waiting times and facilities were also found to be inadequate. The majority of relatives did not like coming back to the ICU to utilize the follow up service.

These findings lead to several changes in practice. Feedback and discussion with doctors and nurses led to raised awareness of the feelings of relatives around the time of death. Guidelines were drawn up for use by medical staff regarding referral to the coroner. ET tubes were subsequently cut off inside the mouth if they were not to be removed. Growth in critical care services has allowed an improvement in facilities for relatives.

In conclusion, those who took advantage of the service found it extremely useful and no formal complaints have since been received. A major concern continues to be that more than 70% of relatives returned to discuss issues surrounding the withdrawal of treatment. Was this their lack of understanding, our lack of explanation or just human nature? Recommendations have now been made; yearly feedback to medical and nursing staff regarding the findings of the service should be formal. A room for appointments away from the unit should be secured. Relatives seen should be contacted after the visit to assess its usefulness in aiding the bereavement process and also the further development of the service.

Keywords: intensive care, bereavement

References

1 Andrew CM. *Intensive Crit Care Nurs* 1998; **3**: 59–65
2 Report of the Working Group. *Guidelines for Bereavement Care in Intensive Care Units*, 1998; 1–31

Is variation in Standardized Mortality Ratio (SMR) determined by case mix?

H. Neill and L. Plenderleith

Department of Anaesthetics, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK

There is evidence from several sources that existing scoring systems do not fully correct for variations in case mix.[1] The Scottish Intensive Care Society Audit Group (SICSAG) collate data collected on consecutive admissions to 22 adult general Intensive Care Units (ICUs) in Scotland. In the Scottish database, the Standardized Mortality Ratio (SMR) for different diagnostic groups varies from 0.49 to 1.35. Different ICUs have different proportions of patients in each diagnostic group and so variation in SMR derived from the APACHE 11 scoring system (AP2) may be partially explained by differences in case mix between units, rendering SMR unhelpful as a measure to compare unit performance.

To examine the possible effect of variation in case mix we obtained the number of patients in each diagnostic group for each of the 22 units in the Scottish database. In a hypothetical model to determine the impact of case mix, we calculated 'observed' mortality for each unit by multiplying the number of patients in each diagnostic group in the unit by the percentage mortality of that group in the Scottish database. An overall 'observed' mortality of the Unit was obtained by summation of 'observed' mortality for each of the diagnostic groups. 'Predicted' mortality was derived by multiplying the 'observed' mortality of different groups in each unit by the reciprocal of SMR for that group in the Scottish database and summation as above to obtain an overall 'predicted' mortality for each unit. Finally, we calculated a novel 'SMR' for each unit from these 'predicted' and 'observed' mortality figures. This novel 'SMR' is the value that would be obtained if each unit achieved the same results as the overall Scottish results for each diagnostic group. Any difference in 'SMR' derived by this model is due solely to the different mix of patients in the units (Fig. 17).

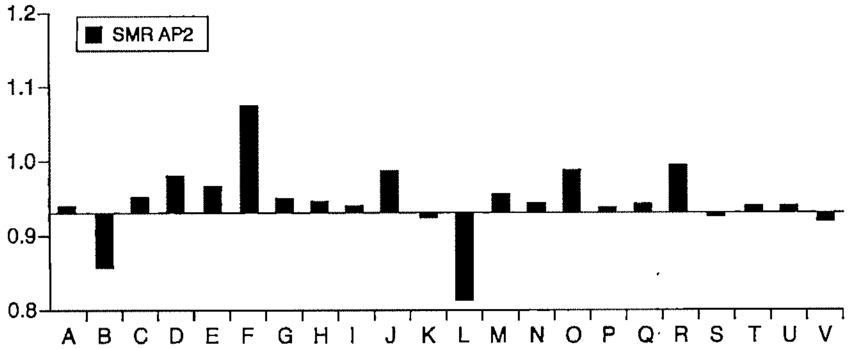

Fig 17 Novel 'SMR' of the 22 units in the SICSAG database (1995–1997; 9848 patients).

The 22 units (A–V) in the SICSAG database have differing 'SMRs' due entirely to a difference in case mix. Differences in SMR values of these units, derived from the APACHE 11 scoring system, may therefore be partly accounted for by case mix variation.

Keywords: statistics, standardized mortality ratio; statistics, scoring systems

Reference

1 Zimmerman JE, Wagner DP, Draper EA, *et al. Crit Care Med* 1998; **26**: 1317–26

Is the measurement of total magnesium obsolete?

G. M. Creed, T. Fox, D. Pierre, R. Beale and R. Leach

Department of Intensive Care, St Thomas' Hospital Guy's and St Thomas NHS Trust, London SE1 7EH, UK

Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation after potassium. Magnesium is an essential activator for more than 300 enzymes (four times more than any other cation), many of which regulate vital processes. Although primarily an intracellular cation, serum magnesium is still considered an important primary measurement to assess magnesium status. Magnesium in blood is about 70% free ionized[1] (biologically active fraction), which has previously been shown[2] to correlate with total magnesium. Ionized magnesium concentrations in critically ill children[3] have demonstrated hypomagnesaemia with normal total magnesium concentrations. Magnesium depletion indicated by low total Mg concentration is frequently corrected by administration of magnesium sulphate. This study investigated the correlation between total and ionized magnesium in the critically ill adult to determine whether therapeutic intervention, based solely on total magnesium, replenishes the biologically active ionized fraction.

Random arterial blood samples (123) from critically ill patients on the ICU at St Thomas' Hospital were analysed for total magnesium using the calmagite reaction on the IL Monarch (Lexington, MA, USA), and ionized magnesium via ion selective electrode on the AVL 988–4 (Graz Austria).

Mean (SD) total magnesium was 1.37 (0.27) mmol litre^{-1} and mean ionized magnesium was 1.04 (0.20) mmol litre^{-1}. Total and serum magnesium significantly correlated (r^2=0.61, P<0.001; Fig. 18). Bland-Altman analysis (Fig. 19) showed mean difference between total and magnesium was 0.33 (0.17) mmol litre^{-1} with limits of agreement 0.0–0.66 mmol litre^{-1}.

Although total and ionized magnesium demonstrated significant correlation, Bland-Altman analysis showed wide variation across

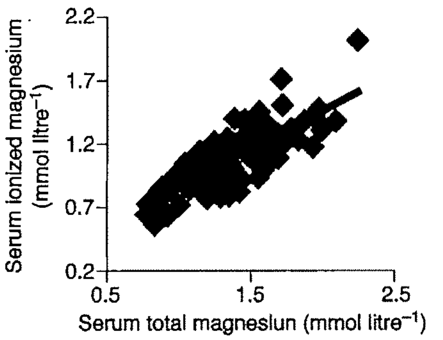

Fig 18 Correlation between serum total magensium and ionized magnesium.

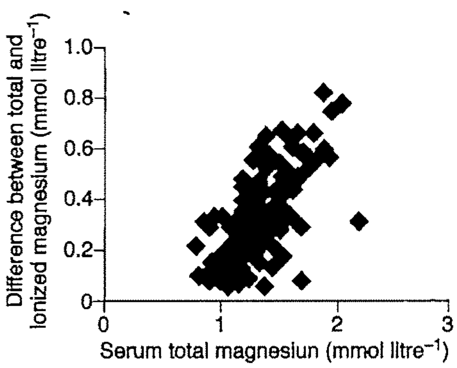

Fig 19 Bland-Altman plot illustrating difference between serum total magnesium and ionized magnesium.

the patient range. The biologically active ionized fraction of magnesium cannot be postulated with any degree of certainty by the total serum magnesium concentration and therapy to correct magnesium depletion should not be based on total magnesium. Total magnesium to determined magnesium depletion is, therefore, obsolete.

Keywords: ions, magnesium

References

1 Toffaletti J. *Am J Chem Pathol* 1995; **104** (Suppl 1): S88–S93
2 Saha H, Harmoinen A. *Clin Chem Lab Med* 1998; **36**: 716–8
3 Fiser RT, Torres A, Butch AW, Valentine JL. *Crit Care Med* 1998; **26**: 2048–52

A prospective audit of enteral feeding within a busy district general hospital intensive care unit in the UK

O. J. Warner, C. Jones and C. Waldman

The Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK

Enteral feeding is now regarded as the 'gold standard' for nutrition support in the intensive care unit. Failure to initiate enteral feeding should be regarded as failure to support a vital organ. We investigated the reasons why enteral feeding was not commenced in timely fashion and why, once established, it was interrupted.

Consecutive prospective admissions to the ICU were studied over a 3-month period. The nursing staff collected all data. Patients' details of specialty, diagnosis, the interval between ICU admission and starting enteral feeding as well as other data were collected. Time of interruption of feeding, and the reasons were also recorded. Data were only collected if the patients were admitted for greater than 24 h.

Fifty-nine patients were studied but nine were excluded because they received an oral diet. Of the 50 patients, 21 (51%) were medical, 15 (36%) were surgical, and 5 (12%) were orthopaedic. Nine (21%) patients were not fed while on the ICU because of clinician preference in 44% of cases. Seventy-eight per cent of patients absorbed their feed on the first day and of those not absorbing, 79% had their aspirates replaced according to the standard procedure. Of those who received enteral support, 20 (48%) had a delay of greater than 12 h before commencing enteral feeding and four patients waited for 48 h. In 55% of these cases, delay was because of clinician's preference. Surgical specialties were most likely to prevent the introduction of enteral support (87%).

Twenty-four per cent of those patients receiving enteral support had their feeds interrupted. The commonest reasons for this include nausea and vomiting (38%), percutaneous tracheostomy insertion (20%), and transfer for CAT Scan (6%). Eighty-two per cent of patients not absorbing their feed received prokinetic agents.

Despite increasing evidence for improved outcome for patients who receive enteral support from previous research, we have shown that there are still significant numbers of patients who are denied this benefit. This appears to be largely a result of the admitting clinician's preference. The authors suggest that decisions of this nature require a multidisciplinary approach.

Keywords: intensive care, enteral feeding

Patient satisfaction with specialist ICU follow-up

K. C. Hames, M. Gager and C. S. Waldmann

Intensive Care Unit, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK

The value of specialist ICU follow-up clinics is now more widely accepted and indeed recommended by the recent Audit Commission Report into the provision of critical care services.[1] The question remains whether patients themselves find such follow up of benefit. We have looked at patient's attitude to our follow up clinic and assessed the specific areas of benefit it has offered them.

A four-point questionnaire was distributed to all patients completing their three follow-up visits to the clinic over a period of 22 months. The questions covered are set out in Table 39.

Table 39 The questions asked during ICU follow up

1. Did you feel that, overall, you benefited from attending the ICU Follow-Up Clinic?
2. Specifically which of the following did you find beneficial?
- A chance to discuss your problems
- Having your questions answered
- Counselling
- Referral to other specialists
- Helping the ICU staff
- Coming back to visit ICU
- Receiving a diary of your stay in ICU
- Any other benefits

3. Can you suggest how the Clinic would have been more benefit to you?
4. If a friend or relative of yours were a patient in ICU, would you recommend they attend an ICU Clinic?

The response rate was 99% (65/66); 99% of these gained some benefit (77% a great deal and 22% a little); 94% indicated that they would recommend the clinic to a relative or friend. Specifically, 80% benefited from having questions answered, 76% from having a chance to discuss their problems, 26% from counselling, 28% from referral to other specialists and 48% felt they had helped the ICU staff. Although not all patients were asked about gaining benefit from returning to visit the unit, 24% of those who were, felt they had done so and 24% appreciated receiving a diary. A further 20% indicated that they would have benefitted from a diary of their stay had it been offered. The questionnaires were liberally annotated with comments including indications that the clinic helped to fill in lost time while under sedation, offered explanations and reassurance about experiences hence removing a sense of isolation. They found follow-up tests reassuring and appreciated the opportunity to say thank-you.

From these findings, it can be indisputably concluded that the clinic offers a number of highly valued benefits to the patient recovering from a period in ICU. The specific benefits highlighted and the comments made by the patients support the view that specialists in ICU can offer help to these patients that cannot be adequately addressed by GPs or other specialists.

Keywords: intensive care, follow up

Reference

1 *Audit Commission National Report, Critical to Success*, October 1999

Subarachnoid haemorrhage affects QT interval length and QT dispersion

J. McViety[2] and **D. C. Bryden**[1]

[1]*Department of Anaesthesia, Hope Hospital, Stott Lane, Salford M6 8HD, UK.* [2]*University of Manchester, Stopford Building, Oxford Road, Manchester, UK*

ECG abnormalities are frequently noted after subarachnoid haemorrhage (SAH), but unlike in cardiac disease their usefulness as markers of cardiac risk is unclear. QT interval prolongation and QT interval dispersion (QT_d) in excess of 50 ms have been proposed as useful markers of cardiovascular mortality in patients with cardiac disease.[1] QT_d is, however, difficult and time consuming to measure. No correlation has been shown between QT interval length and QT dispersion in the healthy population, but the link between QT interval length and QT dispersion after SAH is not clear. The aim of this study was to determine the relationship between QT interval length and QT_d uncorrected and corrected for heart rate (QT_d, QT_{dc}) and the presence of other ECG abnormalities after SAH.

Notes from 77 patients with angiographically proven SAH admitted to our unit over a 6-month period were reviewed. Forty-two sets of notes contained ECGs of suitable quality for interpretation. Each ECG was examined for predetermined ECG abnormalities. QT interval and QT dispersion were measured using the standard manual method.[2] To enable parametric statistical analysis log transformation of the data for QT dispersion was performed.

Following SAH mean values of QT interval (409.8 ms, 95% CI 391.1–428.6) were within the accepted normal ranges but rate corrected QT_c values were prolonged (449.3, 95% CI 434.9–463.7). Geometric means for both QT_d (65.3 ms) and QT dispersion corrected for heart rate, QT_{dc} (72.0 ms) were above the upper limit of normal of 50 ms.

There was a direct relationship between the maximum QT interval length and QT dispersion when corrected for rate (Fig. 20).

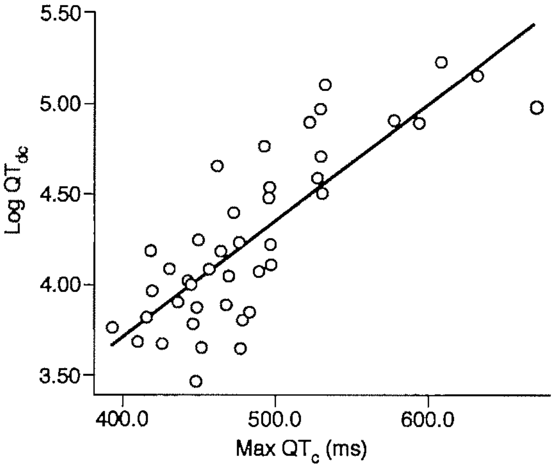

Fig 20 QT analysis following subarachnoid haemorrhage.

Pearson correlation coefficient between log QT_{dc} and the maximum QT_c across each of the 12 leads was 0.816 ($P<0.001$).

No relationship was indentified between ECG abnormality scores and QT dispersion.

When corrected for heart rate, QT interval and QT dispersion are increased after SAH, but do not relate to the number of ECG abnormalities present within the ECG. The longest QT interval measured across the 12 lead ECG (QT_{max}) parallels QT dispersion and is easier and quicker to measure.

Keywords: monitoring, electrocardiography; complications, subarachnoid haemorrhage

Funding: Assessment of heart rate variability after SAH is supported by an Intensive Care Society grant.

References

1 Okin PM, Devereux RB, Howard BV, *et al. Circulation* 2000; **101**: 61–6
2 Pye M, Quinn AC, Cobbe SM. *Br Heart J* 1994; **71**: 511–4

Emergence of antimicrobial resistance in a paediatric intensive care unit

P. B. Baines, N. Taylor, R. E. Sarginson, A. Selby and H. K. F. van Saene

PICU and Medical Microbiology, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP, UK

Antibiotic resistance is an increasing concern in intensive care. Antibiotic restriction does not prevent resistance.[1] A procedure of microbiological surveillance, older systemic antibiotics and oral non-absorbable antimicrobials reduces injections.[2] We studied bacterial resistance with this approach.

We conducted a prospective observational cohort of children with >4 day Paediatric Intensive Care Unit (PICU) admission. Oropharyngeal and rectal swabs were taken on admission then twice weekly, distinguishing carriage on admission ('import') from acquired carriage ('nosocomial'). Oral polymyxin-E/tobramycin/amphotericin B was started when abnormal flora was demonstrated. Oral vancomycin was added for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage.

Over 12 months a total of 353 patients (median age 3 months, median risk of mortality (PIM) 0.07, median stay 8 day) were responsible for 390 admissions resulting in 4688 PICU days; 46% were medical, 38% cardiac, and 26% general surgical. On average per month, 20 full days of glycopeptide therapy were dispensed per 100 patient days (i.e. a monthly density of 20%).

Cephalosporins and aminoglycosides were administered at a monthly density of 50 and 40%, respectively. During all but 3 months, the monthly density of topical polymyxin E, tobramycin, amphotericin B, and vancomycin was higher (at 60%) than the density of the parenteral antimicrobials. Systemic antifungals were administered to five patients over 1 yr. The predominant resistant bacteria carried in the gut were: MRSA, *Enterobacter* and *Citrobacter* species resistant to ceftazidime, *Klebsiella* and *Enterobacter* species resistant to tobramycin. Sixty per cent of them were imported. The carriage density varied between 1.27 and 3.46. A total of eight patients had 12 infections as a result of resistant micro-organisms, MRSA, *Klebsiella* and *Psuedomonas aeruginosa*.

The low rate of carriage and infections with resistant micro-organisms compared with traditional units[1] supports microbiological surveillance and SDD as a way to prevent the development of antimicrobial resistance.

Keywords: intensive care, paediatric; intensive care, infections; antibiotics, resistance

References

1 Toltzis P, Yamashita T, Vilt L, *et al. Crit Care Med* 1998; **26**: 1893–9
2 D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. *BMJ* 1998; **316**: 1275–85

Emergency abdominal aortic aneurysm surgery. Validation of a scoring system

S. P. Hutchinson, M. J. Heap and N. Coad

Northern General Hospital, Herries Road, Sheffield S5 7AU, UK

Survival after emergency abdominal aortic aneurysm surgery is poor with mortality figures of 30–70%. However, long-term survival for those who recover from the initial insult is good. The majority of patients presenting in this situation are, therefore, treated expectantly in the first instance. The cost of their subsequent management is excessive if continued aggressive treatment will prove futile. Objective prognostic estimates may be useful as adjuncts to the clinical decision making in this group of critically ill patients. A simplified risk score has been devised by Urwin and Ridley[1] that may predict 100-day mortality after emergency abdominal aortic aneurysm surgery

Risk score=age+(blood loss in litres×3) − (systolic arterial pressure on admission/10).

We have attempted to validate this scoring system from a retrospective study in our centre.

Coding inaccuracies resulted in the exclusion of some (28) patients that were not emergency abdominal aortic aneurysm operations. Some notes (19 patients) could not be retrieved, and further patients (18) were excluded if there was insufficient recorded information to allow calculation of a risk score; 112 complete patient records were used to produce a dataset. Information was collated in a Microsoft Access database and subsequently manipulated to derive scores in Microsoft Excel. SPSS was used for statistical analysis (Table 40).

Table 40 One hundred-day mortality stratified by risk score group from Urwin and Ridley,[1] compared with our patients

Risk score	<49	50–59	60–69	70–79	>80
Urwin and Ridley[1]	0%	33.3%	53.3%	86.5%	96.5%
Sheffield	0%	33.3%	14.8%	50.0%	78.8%

Substantial differences in mortality exist in several risk score groups. Testing the predictive performance of this score using the Hosmer-Lemeshow goodness of fit statistic for our mortality data, we find a very poor fit ($P<0.01$), and an area under the receiver operating characteristic curve of 0.75.

This study has failed to validate the scoring system devised by Urwin and Ridley[1] and illustrates the risks of extrapolating data from one centre to another. Differences in case mix and surgical practice are evident within the raw data and will account for the differences in mortality. On-going prospective audit in our centre will allow validation of a scoring system based on our population, but its purpose should probably be limited to internal audit rather than for influencing decisions regarding patient outcome.

Keywords: surgery, abdominal; statistics, scoring system

Reference

1 Urwin SC, Ridley SA. *Anaesthesia* 1999; **54**: 739–44

Incidence of bacteraemia, severity of illness and outcome: a 6-month prospective audit

A. Corona[1], P. Wilson[2] and M. Singer[1]

[1]*Bloomsbury Institute of Intensive Care Medicine and* [2]*Department of Microbiology, University College, London W1N 8AA, UK*

We sought to discover the incidence of community ward- and ICU-acquired bacteraemia in our 22-bed ICU, in conjunction with the concurrent severity of illness of the patients, the type of antibiotic therapy (Rx) administered, and their ICU outcome.

Patient characteristics, clinical and outcome data were collected on all patients admitted to the ICU over a 6-month period (February to July 2000). The presence and timing of positive blood cultures, plus the response and duration of Rx were recorded. C is defined as a bacteraemia acquired outside hospital; W for a ward patient developing bacteraemia within 72 h of ICU admission, and bacteraemia for those occurring subsequently.

Patients (713, 455 male, 258 female; 54% medical, median age 62 (range 3–96), first 24 h APACHE II score, 16 (range 2–43), ICU

Table 41 Patient demographics and clinical outcome following bacteraemia acquired outside hospital (C), on the ward (W) or ICU. *Data only refer to first episode of bacteraemia. **Contingency coefficient

	C (14 pts)	W (28 pts)	ICU 49 pts*	*P* value**
Gram+/Gram− /Polymicrobial/Yeast	8/4/1/1	12/6/8/2	19/23/6/1	0.268
Bacteraemia onset day; median (range)	1 (−6 to 0)	1 (−6 to 0)	7 (3–20)	
Septic shock/severe sepsis/sepsis/bacteraemia	8/5/1/0	21/2/5/0	18/10/19/2	<0.05
SOFA score on starting Rx; median (range)	10 (0–19)	9.5 (1–19)	6 (1–16)	0.139
SOFA score at end of Rx; median (range)	2.5 (0–20)	7 (0–20)	4 (0–20)	0.639
Duration of Rx; median (range)	5.5 (3–28)	5 (3–14)	5 (2–14)	
Antibiotic mono-Rx/combination Rx	8/6	22/4	41/4	
ICU stay; median (range)	4.5 (2–24)	7 (1–18)	24 (4–66)	<0.0001
ICU mortality; median (range)	4 (29%)	14 (50%)	22 (45%)	0.190

stay 4.5 days (range 1–66) and ICU mortality 20.1%) were admitted over the study period. Fourteen (2.2%) patients experienced C; 28 (4.4%) W and 49 patients (6.8%) suffered 60 episodes of ICU bacteraemia. One patient experienced both C and W bacteraemias while six had both W and ICU bacteraemias (Table 41).

For Gram+, *Staphylococcus aureus* was the leading isolate for C (5) and W (6); coagulase-negative *Staphylococcus* for ICU bacteraemia (16). For Gram–, *Escherichia coli* was the main isolate for C (4) and W (3); *Klebsiella* spp. (14) for ICU bacteraemia. Of 10 fungaemias (including six polymicrobial), seven were ward associated; the most frequent isolate being *Candida glabrata*. Septic shock complicated 57% C, 75% W and 38% ICU bacteraemias; the main sources were endocarditis (3) for C, and line-related for W (6) and ICU (29) bacteraemia. The majority of bacteraemias were successfully treated with short courses of monotherapy.

Such data inform practice and are useful for drawing comparisons between ICUs.

Keywords: infection, bacteraemia; infection, fungaemia

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